SECTION 2

RISK ASSESSMENT METHODS

2.1 INTRODUCTION

The presentation of risk assessment methods in this section follows the format of the risk assessment process recommended by EPA for cancer and noncancer toxicity:

- Hazard identification
- Dose-response assessment
- Exposure assessment
- Risk characterization (U.S. EPA, 1986a,c; IRIS, 1997).

EPA methods follow the outline developed in the National Academy of Sciences (NAS) report entitled *Risk Assessment in the Federal Government: Managing the Process* (NAS, 1983; see Figure 2-1). According to the NAS,

> . . . risk assessment can be divided into four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. A risk assessment might stop with the first step, hazard identification, if no adverse effect is found or if an agency elects to take regulatory action without further analysis, for reasons of policy or statutory mandate. (NAS, 1983)

Readers may wish to consult the new NAS document, *Science and Judgement in Risk Assessment*, which updates and expands the 1983 work (NAS, 1994).

Hazard identification is the first step in the risk assessment process. It consists of a review of biological, chemical, and exposure information bearing on the potential for an agent to pose a specific hazard (Preuss and Erlich, 1986). Hazard identification involves gathering and evaluating data on the types of health effects associated with chemicals of concern under specific exposure conditions (e.g., chronic, acute, airborne, or foodborne) (U.S. EPA, 1985).

Section 2.2 provides an overview and summary of the hazard identification process and specific information on hazard identification for chemical

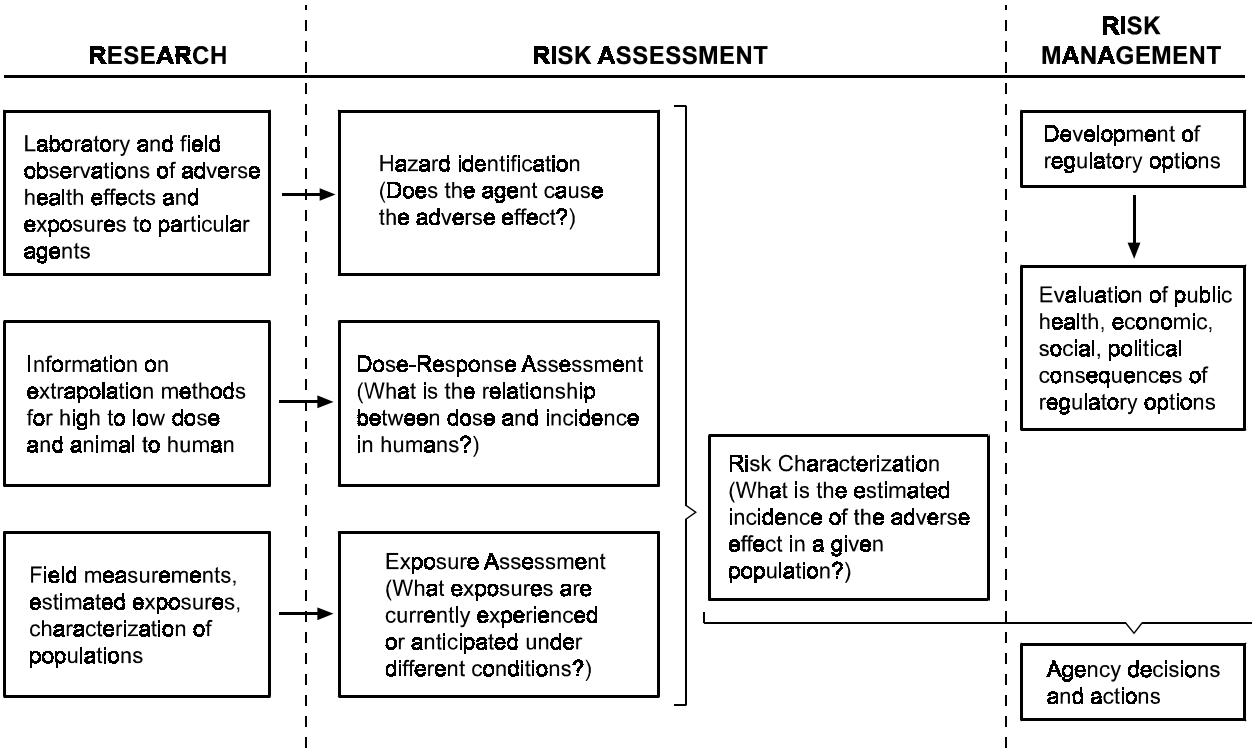


Figure 2-1. Elements of Risk Assessment and Risk Management (NAS, 1983).

contaminants in noncommercially caught fish. It does not provide detailed guidance on hazard identification since EPA's Office of Water has already completed the hazard identification step with respect to fish contaminants. This work was undertaken to identify the fish contamination target analytes of concern, as described in *Volume 1: Fish Sampling and Analysis* (U.S. EPA, 1993a, 1995) in this guidance series. This process included an evaluation of information on toxicity, occurrence, persistence, and other factors. The methods for selecting the highest priority chemicals as target analytes are described in Volume 1 and summarized briefly in Section 2.2.1 of this document.

The second step in the risk assessment process is the evaluation of the dose-response dynamics for chemicals of concern (see Section 2.3). The dose-response dynamic expresses the relationship between exposure and health effects. To evaluate this relationship, the results of human and animal studies are reviewed; the dose-response evaluation may focus on specific types of effects (e.g., developmental, carcinogenic) or be designed to encompass all adverse effects that could occur under any plausible scenario.

The third step in the risk assessment process is exposure assessment (see Section 2.4). Individual exposure assessments use data on chemical residues in fish and human consumption patterns to estimate exposure for hypothetical individuals. Population exposure assessments consider the distributions of

exposure in a population. Exposure assessments are then combined with dose-response data to determine risk.

The final step in risk assessment is risk characterization (see Section 2.5), which provides an estimate of the overall individual or population risks. Risk characterization can be used by risk managers to prioritize resource allocation and identify specific at-risk populations; it is also used to establish regulations or guidelines and to estimate individual or population risk. In this document, risk characterization involves developing the risk-based consumption limits provided in Section 4. When risk characterization is used to estimate individual or population risk, it provides the risk manager with necessary information concerning the probable nature and distribution of health risks associated with various co-ntaminants and contaminant levels.

The importance of describing and, when possible, quantifying the uncertainties and assumptions inherent in risk assessment has been long recognized, though not consistently practiced (Habicht, 1992). Uncertainty analysis is particularly critical in risk characterization and must be performed throughout the risk assessment process to adequately characterize assumptions in this last step of the process. Consequently, various sources of uncertainty are described and assumptions are discussed for each of the four activities that constitute risk assessment.

2.1.1 Other Information Sources

This document focuses on risk assessment as it applies primarily to fish advisories. EPA has issued several detailed guidelines for conducting specific portions of the risk assessment process, which address the following areas:

- Exposure assessment (U.S. EPA, 1992a)
- Carcinogenicity risk assessment (U.S. EPA, 1986a, 1996d)
- Mutagenicity risk assessment (U.S. EPA, 1986c)
- Developmental toxicity risk assessment (U.S. EPA, 1991a)
- Assessment of female and male reproductive risk (U.S. EPA, 1996c)
- Health risk assessment of chemical mixtures (U.S. EPA, 1986d)
- Exposure factors (U.S. EPA, 1990a).

These guidelines were developed by EPA to ensure consistency and quality among Agency risk assessments. EPA's Risk Assessment Forum is in the process of developing quantitative guidelines on dose-response assessment of systemic toxicants. One approach used to estimate reference doses for chronic exposure toxicity is presented in the Background Documents for IRIS. It is also found in many EPA publications and has been summarized in recent papers that discuss risk assessment within EPA (e.g., Abernathy and Roberts, 1994; Barnes and Dourson, 1988). Relevant sections of each of the above guidelines were consulted in developing this section, along with other resources cited throughout the section. Additional references are listed in Section 7 and Appendix A.

2.2 HAZARD IDENTIFICATION

Hazard identification assesses the likelihood that exposure to specific chemicals under defined exposure conditions will pose a threat to human health. Hazard identification is often used effectively to determine whether a chemical or groups of chemicals occurring in a specific exposure situation require action. It has been narrowly defined for some applications to provide only chemical-specific hazard data (NAS, 1983). However, in the new NAS document, *Science and Judgement in Risk Assessment*, the use of an iterative approach to evaluating risk is emphasized, which entails the use of relatively inexpensive screening techniques to determine when to proceed to more in-depth evaluations (NAS, 1994). This is analogous, in practice, to what is already frequently done at the State and local level. The early stages of risk assessment often include consideration of the existence or likelihood of exposure to determine the need for further work on a chemical. At the State, local, and Tribal organization levels, administrators and risk managers concurrently evaluate both the hazard and the occurrence of chemicals to assess whether sufficient risk exists to justify an investment of time and resources in further action. Their needs for information to guide further action are, therefore, different from that of a Federal agency, which may evaluate hazards independently of exposure considerations.

A preliminary risk evaluation typically precedes an in-depth risk assessment because most States, localities, and Tribal organizations do not have the resources to conduct detailed risk analyses in the absence of information indicating that health risks may occur. Thus, this section discusses hazard identification as an approach to making preliminary decisions regarding further action on fish advisories. This approach is similar to the screening methodology used for the identification of the 25 target analytes addressed in this guidance series and is discussed in *Volume 1: Sampling and Analysis* in this series (U.S. EPA, 1995).

Although hazard identification is essentially a screening process, it may entail a complex evaluation of the exposure scenarios and toxicological and biological properties of contaminants (e.g., bioavailability, degradation, existence of breakdown products and metabolites). Hazard identification ranges in scope from the use of existing summary data (e.g., IRIS or Agency for Toxic Substance and Disease Registry [ATSDR] Toxicological Profiles) to a detailed evaluation of each aspect of exposure and risk; the depth of analysis is usually determined by time and resource availability. For example, an evaluation of a contaminant's toxicological properties may include an analysis of all health endpoints likely to occur in the exposure scenarios of concern. Recent EPA guidance (Habicht, 1992) describes hazard identification as:

> . . . a qualitative description based on factors such as the kind and quality of data on humans or laboratory animals, the availability of ancillary information (e.g., structure-activity analysis, genetic toxicity, pharmacokinetics) from other studies, and the weight-of-evidence from all of these data sources.

Under some circumstances, extensive data collection may be undertaken. For example, to evaluate carcinogenic risk, EPA has recommended the following information be reviewed in a hazard identification: physical-chemical properties, routes and patterns of exposure, structure-activity relationships, metabolic and pharmacokinetic properties, toxicological effects (including subchronic and chronic effects, interactions with other chemicals, pathophysiological reactions, and time-to-response analysis), short-term tests (including mutagenicity and DNA damage assessment), long-term animal studies, human studies, and weight-of-evidence (U.S. EPA, 1986a). At the State, local, and Tribal organization level, this type of in-depth analysis is rarely carried out for each health endpoint of a chemical hazard, due to the time and resources required. Alternatively, databases such as IRIS and the Hazardous Substances Data Bank (HSDB), which summarize health endpoints and associated risk values, are inexpensive, readily available, and often consulted in the development of a hazard profile.

2.2.1 Approach for Fish Contaminants

The hazard identification step in risk assessment of chemically contaminated fish has been refined by EPA through careful review of the chemical characteristics considered to be critical in determining human health risk. These parameters are:

- High persistence in the aquatic environment
- High bioaccumulation potential
- Known sources of contaminant in areas of interest
- High potential toxicity to humans
- High concentrations of contaminants in previous samples of fish or shellfish from areas of interest (U.S. EPA, 1989a).

These characteristics are described in detail in *Volume 1: Fish Sampling and Analysis* in this series. Additional information on persistence and bioaccumulation potential may be obtained from EPA documents such as the *Technical Support Document for Water Quality-Based Toxics Control* from the Office of Water (U.S. EPA, 1991b), which contains a brief description of the bioaccumulation characteristics considered for the development of reference ambient concentrations (RAC). Readers may also wish to consult the open literature (e.g., Callahan et al., 1979; Lyman et al., 1982).

2.2.1.1 Toxicological Data—

The toxicity of a chemical to humans can be evaluated based on its acute (short-term) exposure toxicity and/or chronic (long-term) exposure toxicity. The chronic toxicity of a chemical is usually of primary concern for environmental toxicants; however, the varied consumption patterns of fish consumers complicate the analysis of fish contaminants. This issue is discussed in Section 2.4 in additional detail. There are a number of databases that contain risk values for various types of chronic toxicity (e.g., carcinogenicity, liver toxicity, and neurotoxicity). IRIS is a widely accepted data source due to the extensive review conducted on the risk values contained in the database. EPA's Health Effects Assessment Summary

Tables (HEAST) are also frequently used (HEAST, 1992). Other relevant databases include HSDB, the National Cancer Institute's Chemical Carcinogenesis Research Information System (CCRIS), EPA's GENE-TOX, and the National Institute of Occupational Safety and Health's (NIOSH's) Registry of Toxic Effects of Chemical Substances (RTECS). All of the above databases except HEAST are available through TOXNET.* ATSDR's Toxicity Profiles also provide detailed toxicity data summaries.

2.2.1.2 Contaminant Data—

Information on the prevalence and measured concentrations of fish contamination has been generated through numerous sampling and analysis programs. EPA has provided a summary of preliminary screening results on the prevalence of selected bioaccumulative pollutants in fish and shellfish in Volume I of the *National Study of Chemical Residues in Fish* (U.S. EPA, 1992b). In addition, substantial guidance is provided in Volume 1 of this series on planning a sampling strategy and conducting fish contaminant analyses (U.S. EPA, 1995).

Likely sources of contaminants are often known to State, Regional, and Tribal officials or can be identified through a review of data on manufacturing, toxic releases, or complaints regarding contamination of food, air, water, or soil. Recommended sources and lists for obtaining data on probable contaminants include

- EPA-recommended target analytes (see Table 1-1)
- Chemical releases reported in EPA's Toxics Release Inventory (TRI) database
- The Manufacturers' Index
- EPA priority pollutants
- State inventories of manufacturers and operations
- Chemicals identified in industrial and publicly owned treatment works (POTW) effluents as nonbiodegradable
- Known spills and contaminants (as reported under the Comprehensive Environmental Response, Compensation, and Liability Act [CERCLA] to the Office of Emergency and Remedial Response)
- EPA source inventory for contaminated sediments
- ATSDR's HAZDAT database
- Listing of Superfund (National Priority List) sites

* TOXNET is managed by the U.S. Department of Health and Human Services' National Library of Medicine (Bethesda, MD). For more information, call (800) 848-8990 (for Compuserve), (800) 336-0437 (for Telenet), (800) 336-0149 (for TYMNET), or (301) 496-6531 for technical assistance.

- Common-use chemicals based on practices in the State or region (e.g., agriculture or fuels).

This information can be used to describe local waterbodies, incorporating geographic and source-specific data. The geographic distribution of potential contaminants can be used to guide the selection of monitoring sites for sampling and analysis of potentially contaminated fish.

Volume II of the *National Study of Chemical Residues in Fish* (U.S. EPA, 1992b) provides an example of how information on the first three characteristics of chemical contaminants (high persistence in the aquatic environment, high bioaccumulation potential, and high concentrations of contaminants in previous samples of fish or shellfish from areas of interest) can be summarized to form the basis for a hazard evaluation. The document summarizes the results of the National Bioaccumulation Study, correlates contaminant prevalence with sources of pollutants, and briefly describes the chemical and toxicological properties of 37 chemicals and chemical groups (U.S. EPA, 1992b).

2.2.1.3 Sources of Exposure—

Hazard identification may also include a comprehensive evaluation of all sources of exposure, including those that augment the primary exposure of concern, to obtain an estimate of total exposure. For fish contaminants, a comprehensive exposure evaluation would involve an evaluation of exposures from other sources such as air, water, soil, the workplace, or other foods, including commercially caught fish. In some cases, in fact, other routes of exposure may contribute more to overall contaminant body burden than does contaminated noncommercially caught fish. It is beyond the scope of this guidance document to provide detailed direction on evaluating exposures occurring via other media; however, readers are encouraged to assess other sources of exposures in their hazard evaluations (see Section 2.4.5.6 for additional information).

If exposure from noncommercially caught fish consumption were added to already elevated exposure levels arising from other sources, it could produce an overall exposure associated with adverse health effects. Under such circumstances, a more stringent fish consumption limit (or some other risk management option) may be needed. Readers may wish to determine whether such an evaluation is warranted through consideration of the likelihood that exposures are occurring via nonfish routes and the availability of data and resources to carry out a comprehensive exposure evaluation.

EPA's Office of Water, in conjunction with the Interagency Relative Source Contribution Policy Workgroup, is currently developing guidance on the use of a Relative Source Contribution (RSC) approach. According to the preliminary information available on this approach:

> The RSC concept could be used in fish advisory activities. The amount of exposure from fish consumed is determined along with

the estimated exposure from all other relevant sources (e.g., drinking water, food, air, and soil) for the chemical of concern. By comparing the overall exposure with the Reference Dose, it can then be determined whether the amount of total exposure to the chemical may result in an adverse effect and warnings can be issued regarding the safety of consuming such fish (Borum, 1994).

The CERCLA office at EPA, which offers assistance on multimedia assessments of hazardous waste sites, may also be consulted for information on methods to estimate background levels of various contaminants. They have developed guidance documents that may be useful to those readers who plan to conduct comprehensive exposure assessments. See Appendix A for a listing of sources of additional information.

2.2.2 Assumptions and Uncertainty Analysis

Hazard identification, as described in this guidance, is a screening process used to select the chemicals and exposure scenarios of greatest concern. As a screening process, it uses simplifications and assumptions in each step of the process. Because each aspect of hazard is not examined in its entirety, the process generates some uncertainty.

Uncertainty is introduced by the variability in persistence and bioaccumulation potential of chemicals that may occur in untested media. The behavior of chemicals in all types of media cannot be anticipated. Interactions of the target analytes in sediments containing multiple chemical contaminants may cause chemicals to change their forms as well as their bioaccumulation and persistence characteristics. For example, binding of the target analyte to organic matter may cause it to become more or less persistent or available for bioaccumulation, or decomposition may occur, producing metabolites that have significantly different properties than those of the original target analyte. These chemical and biological interactions are more likely to occur in a complex system (e.g., a hazardous waste site), with relatively unstable chemicals, and with metals having multiple valence states.

The persistence of a chemical in the aquatic environment and its bioaccumulative potential are based on its physical and biochemical properties. Although the critical information is available for many chemicals of concern, it is not available for all chemicals. For example, chemicals that have been recently introduced into the environment may not be well characterized in terms of their persistence and bioaccumulation potential. Consequently, there is the potential for under- or overestimating the risk they pose to human health.

Estimation of chemical toxicity can be a source of significant uncertainty in the hazard identification process. A toxicity evaluation incorporates data on a variety of health endpoints and usually requires that human toxicity estimates be derived from studies in experimental animals. There are often insufficient data in the toxicological literature to fully characterize the toxicity of a chemical. Some types

of toxicity are well-described in the toxicological and risk literature. Others, such as developmental toxicity, neurotoxicity, and immunotoxicity, have only recently become subjects of intensive research. Although studies of developmental toxicity date from the 19th century, there has been a dramatic increase in both epidemiological and toxicological studies in recent years. Consequently, there are limited data for most chemicals on these types of effects. Uncertainties associated with toxicity and health risk values (e.g., q_1*s and RfDs) are discussed in Section 2.3.

The two remaining characteristics of hazard identification (known sources of contaminants in areas of interest and high concentrations of contaminants in previous samples of fish or shellfish) are excellent indicators of potential hazard. A major uncertainty associated with these characteristics arises from the potential for omitting from sampling programs areas not known to be contaminated. During an era of limited resources, it is a common, but not necessarily valid, assumption that known contaminated areas should be the focus of evaluation and action. Given an array of known contaminated sites, attempts to identify additional contamination may appear unnecessary. However, it is recommended that readers conduct a detailed review of potential contamination sources for all waterbodies before determining whether or not adequate hazard identifications have been conducted.

Because the goal of the risk assessment process is protection of human health, it is typically designed to provide the maximum protection against underestimating risk. Therefore, the hazard identification step in the risk assessment process may result in the inclusion of chemicals or exposure situations that, later in the process, are found not to pose significant health risks. This type of approach is taken because the consequences of underestimating risk, or excluding a chemical that poses a public health hazard, are potentially more serious than the consequences of overestimating risk at this early stage of evaluation.

The hazard identification process forms the basis for decisions regarding those chemicals and exposure scenarios that warrant further analysis. It entails the collection and evaluation of information regarding toxicity, bioaccumulation potential, persistence, and prevalence. Although there is uncertainty associated with this aspect of the assessment, quantitative evaluation of the uncertainty can best be conducted in later steps in the risk assessment process. Because each aspect of hazard identification is carried out in more detail in the risk assessment steps that follow, the uncertainties and assumptions can be better refined and quantified during subsequent steps. The information generated on toxicity and exposure in this process also serves as the basis for the subsequent dose-response evaluation and exposure assessment steps in the risk assessment.

2.3 DOSE-RESPONSE ASSESSMENT

This section briefly outlines the current EPA methodology for carrying out a dose-response assessment. Additional information on dose-response evaluations is available in the references cited in Section 7 and Appendix A.

A dose-response relationship expresses the correlation between exposure and health effects. To evaluate this relationship, the results of human and animal studies with controlled and quantified exposures are reviewed. This evaluation may focus on specific types of health effects or be designed to encompass all adverse effects that could occur under any plausible exposure scenario. Dose-response evaluations result in the derivation of toxicity values such as cancer potencies and reference doses.

Actual fish consumption patterns may not correspond well to the typical periods of exposure studied in toxicity tests (i.e., acute or chronic exposure). Many fish consumers ingest intermittent doses of varying sizes and may consume fish over a short period of time (e.g., a vacation) or on a regular basis over a lifetime. The potentially large, intermittent dose (bolus dose) has not been evaluated in most toxicity studies. Chronic exposure studies commonly use daily dosing and acute studies may use one or a few very large doses over a very short time period (e.g., 2 to 3 days). Short-term dosing is frequently used in developmental toxicity studies (discussed in Section 2.3.2.3); two of the 25 target analytes have RfDs based on developmental toxicity (methylmercury and PCBs).

Fish consumption patterns are discussed in more detail in Section 2.4.5.4 and Appendix D; however, when developing fish advisories, it is important to be aware that there is no information available on the impact of bolus dosing. The methods used to calculate fish consumption limits allow the daily RfD to be aggregated over a period of time (e.g., 1 month) into one or more meals. Thus the consumption **averaged** over 1 month corresponds to an **average** daily dose indicated by the RfD. However, the actual dose that may be consumed in 1 day can be approximately 30 times (in the case of a 30-day advisory) the daily RfD.

A bolus dose may not be a problem for many individuals; however, it is a concern for those who are particularly susceptible to toxicants. For example, a relatively large single dose may be problematic for those with decreased ability to detoxify chemicals (e.g., children and the elderly) and those with special susceptibilities (e.g., persons taking certain medications, children, and pregnant or lactating women). Potential adverse effects in some groups are noted for many of the target analytes in Section 5. For example, organochlorines may interact with some commonly prescribed pharmaceuticals; consequently, individuals using specific drugs may find the efficacy altered by large doses of contaminants that interact with their drug-metabolizing systems. Infants have an immature immune system and may be less able to detoxify certain chemicals. Children have rapidly developing organ systems that may be more susceptible to disruption. A recent NAS report, *Pesticides in the Diets of Infants and Children* (NAS, 1993), concluded that children up to age 18 are substantially different from adults in the relative immaturity of their biochemical and physiological functions and structural features. These differences can alter responses to pesticides, especially during windows of vulnerability, leading to permanent alteration of the function of organ systems. The authors, who included pediatricians, toxicologists, epidemiologists, and other health specialists, concluded that:

> Infants and children may exhibit unique susceptibility to the toxic effects of pesticides because they are undergoing rapid tissue growth and development, but empirical evidence to support this is mixed
>
> and
>
> Traditional approaches to toxicological risk assessment may not always adequately protect infants and children (NAS, 1993).

Although the focus of the NAS report was on pesticides (many of the target analytes are currently or were formerly used as pesticides), much of the analysis is relevant to other chemical exposures as well. Readers may wish to refer to the NAS report for a more complete discussion of various related topics of interest including neurotoxicity in children, various dosimetry scaling methods, and consumption patterns.

A dose-response evaluation has already been carried out by EPA for the 25 target analytes addressed in this guidance series. These evaluations resulted in the calculation of risk values: either cancer slope factors (q_1*s), reference doses, or both. The risk values used in this work and cited in the toxicological profiles in Section 5 were obtained primarily from EPA's IRIS database. All data searches were carried out in 1997. For chemicals lacking IRIS risk values, values were obtained from EPA's Office of Pesticide Programs (OPP) or EPA's Health Effects Assessment Summary Tables (HEAST, 1992).

A comprehensive dose-response evaluation requires an extensive review of both the primary literature, including journal articles and proceedings, and the secondary literature, such as books, government documents, and summary articles. It is typically very time consuming and requires data evaluation by toxicologists, epidemiologists, and other health professionals. Because risk values are available for the target analytes, it is not recommended that readers undertake further detailed dose-response evaluations for these chemicals. However, new data are continually being generated that may require evaluation. In addition, chemicals that are not included in the target analyte list may require analysis. It is strongly suggested that an evaluation begin with a review of current government documents on a chemical. In many cases, EPA, FDA, or ATSDR conducts detailed dose-response evaluations when a chemical is identified as an environmental pollutant or when new data become available. This may save readers hundreds of hours of research by providing data and risk values.

2.3.1 Carcinogenic Effects

EPA has recently proposed new guidelines for cancer risk assessment (U.S. EPA, 1996d). These guidelines have not been finalized yet but would supersede the existing cancer guidelines (U.S. EPA, 1986d). The following discussion presents information from the existing guidelines that has not changed in the proposed guidelines and highlights information that has changed. EPA (along with many

other risk assessors) takes a probabilistic approach to estimating carcinogenic risks. Cancer risk is assumed to be proportional to cumulative exposure and, at low exposure levels, may be very small or even zero. EPA assumes that carcinogens do not have “safe” thresholds for exposure; that is, any exposure to a carcinogen may pose some cancer risk. Carcinogenic risk is usually expressed as a cancer potency (q_1*) value with units of risk per milligram/kilogram/day exposure. Risk may also be estimated for specific media. When risks in air and water are provided, these are referred to as unit risks because they are expressed as risk per one unit of concentration of the contaminant in air or water.

The cancer slope factor is derived from dose-response data obtained in an epidemiological study or a chronic animal bioassay. Because relatively high doses are used in most human epidemiological studies and animal toxicity studies, the data are usually extrapolated to the low doses expected to be encountered by the general population. The dose-response data from one or more studies are fit to standard cancer risk extrapolation models, which usually incorporate an upper-bound estimate of risk (often the 95 percent upper bound). This provides a margin of safety to account for uncertainty in extrapolating from high to low doses and variations in the animal bioassay data (IRIS, 1997). In the existing guidelines, the model used as a default to calculate the cancer potency is the linearized multistage (LMS) model. Cancer potency is estimated as the 95 percent upper confidence limit of the slope of the dose-response curve in the low-dose region. This method provides an upper estimate of risk; the actual risk may be significantly lower and may be as low as zero. In the proposed cancer guidelines, straight line extrapolation for a linear default is proposed instead of the LMS model. The reason is that the LMS model gave an appearance of specific knowledge and sophistication unwarranted for a default model (U.S. EPA, 1996d).

Cancer potencies may be calculated for both oral and inhalation exposure. There are four major steps in calculating cancer potencies:

- Identify the most appropriate dose-response data
- Modify dose data for interspecies differences
- Develop an equation describing the dose-response relationship
- Calculate an upper confidence bound on the data.

These are described in more detail in the guidelines for cancer risk assessment (U.S. EPA 1986a, 1996d) and in texts on risk assessment. Cancer slope factors are provided for those target analytes that EPA has determined have sufficient data to warrant development of a value. The values are listed in Table 3-1 and discussed in Section 5; they were used to calculate the consumption limits in Section 4.

As discussed in Section 2.3.2.3, children may have special susceptibilities to some chemicals and some types of effects. Exposure to a carcinogen early in life may generate greater risk than exposure later in life. This is due to a variety of factors including the rapid growth and development ongoing in children and the proportionally greater consumption by children of some foods. The experimental

literature on this subject is not conclusive and readers may wish to review the NAS report to obtain additional information (NAS, 1993).

2.3.2 Noncarcinogenic Effects

2.3.2.1 Acute Exposure—

Noncarcinogenic effects that occur over brief periods of time, e.g., a few hours or days, are considered to be acute exposure effects. They do not necessarily result in an acute (immediate) response, and so the exposure and response periods must be considered separately. The pesticide paraquat is an example of a chemical that usually causes no immediate response to acute exposure but often results in fatal outcomes after several days or weeks.

Acute exposures have traditionally been considered primarily in the realm of occupational health or poisoning incidents rather than environmental health because the brief, low-level exposures associated with most environmental exposures do not usually result in overt symptoms. The exceptions to this have been individuals with allergies or chemical sensitivities. However, there has been a very limited analysis of most environmental pollutants with regard to both the nature and the critical dose for acute nonlethal effects. Acute exposures are of concern for fish contaminants due to the ability of fish to bioaccumulate chemical contaminants to fairly high levels and the relatively large and frequent meals (i.e., bolus doses) that may be consumed by sport and subsistence fishers and their families.

The goal of an acute exposure dose-response evaluation is to identify a threshold exposure level below which it is safe to assume no adverse health effects will occur. There are no widely used methods within EPA for setting such exposure levels. Prenatal acute exposures are discussed in the DDT toxicological profile summary in Section 5. Additional guidance on acute exposure risk assessment methods may be provided in future revisions to this document. EPA welcomes comments and recommendations on this and other methodologies.

Most toxicological information currently available on acute exposure is in the form of LD_{50}s from animal studies. These studies identify the (usually single) dose that was lethal to 50 percent of the study animals via a specific exposure route. The data are used primarily to give a qualitative sense of the acute toxicity of a chemical. The information is generally used for purposes of planning industrial and application processes, transportation, handling, disposal, and responses to accidental exposures. The data are also used for regulatory purposes and to select the less-toxic alternatives among a group of chemical options. LD_{50}s may also be used to evaluate ecological toxicity.

LD_{50}s are not easily adaptable to an evaluation of the human response to acute exposures. Because they are focused on the level at which 50 percent of animals die, they do not provide information on other types of toxic responses, including those that led to death. Fatal toxic responses may be substantially different from

the responses observed at lower, but still acutely toxic, doses. The LD_{50} also does not provide information on the exposure threshold for lethality, which is always lower (and may be much lower) than the exposure level required to kill 50 percent of the study subjects. For these reasons, the LD_{50}s have very limited utility in identifying a threshold for effects of acute exposure. LD_{50}s may, however, provide comparative information regarding differences in sensitivity between various age groups or sexes that can be used to evaluate toxicity qualitatively.

Human and veterinary poisoning centers (e.g., Poison Control Centers) are primary sources of data on acute exposure effects and thresholds. The poisoning data are limited, however, in many of the same ways in which LD_{50} data are limited. The severe responses that often lead to the reporting of an incident do not indicate the level at which more moderate responses may occur. In addition, the dose is often not known or is estimated imprecisely. The poisoned individual may have predisposing medical conditions or may have been exposed concurrently to other chemicals (including medicines) that affect the nature of the responses.

EPA's Health Advisories also provide some acute exposure information and guidance regarding 1- and 10-day exposure limits for children with an assumed 10-kg body weight (available from the EPA's Office of Water). The Toxicological Profiles developed by ATSDR contain Minimal Risk Levels (MRLs) for acute effects for some contaminants. Additional information may be obtained from HSDB. A qualitative summary of acute effects and estimated human lethal doses is provided for most target analytes in Section 5.

2.3.2.2 Systemic Effects from Chronic Exposure—

Noncarcinogenic effects resulting from multiple exposures occurring over a significant period of time are also termed chronic exposure effects (IRIS, 1997). For humans, this usually means exposures over months or years. For animals in studies used to evaluate human chronic toxicity, the temporal definition of chronic exposure depends on the species but is usually defined as a significant portion of the animal's life. Chronic studies are reviewed to determine critical effects for specific chemicals. The critical effect is the first adverse effect, or its known precursor, that occurs as the dose rate increases (IRIS, 1997). Subchronic exposures in toxicity studies (usually 3 months to 1 year) may also be used to evaluate chronic toxicity.

To protect against chronic toxicity resulting from exposure to contaminants, EPA has developed RfDs. The RfD is defined as "an estimate (with uncertainty perhaps spanning an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (U.S. EPA, 1987a). The use of IRIS RfDs is recommended for evaluation of chronic exposure toxicity of the target analytes. These are listed in Table 3-1 in Section 3 and again in Section 5. Additional chronic exposure toxicity data for the target analytes are presented in Section 5, with a brief description of how estimated exposure limits could be calculated based on chronic toxicity. Note that the RfDs listed in IRIS are subject to change as new

methodologies and toxicological data become available. Readers are advised to consult the IRIS database to ensure that they are using the most up-to-date toxicity values.

RfDs calculated for chronic noncarcinogenic effects reflect the assumption that, for noncarcinogens and nonmutagens, a threshold exists below which exposure does not cause adverse health effects. This approach is taken for noncarcinogens because it is assumed that, for these types of effects, there are homeostatic, compensating, and adaptive mechanisms that must be overcome before a toxic endpoint is manifested (IRIS, 1997). (Some chemicals such as lead, however, appear to show nonthreshold noncarcinogenic effects.) It is recommended that concern be directed to the most sensitive individuals in a population, with the goal of keeping exposures below calculated RfDs for them (IRIS, 1997). RfDs are generally expressed in terms of milligrams of contaminant per kilogram consumer body weight per day (mg/kg/d).

There are two major steps to calculating RfDs: (1) identify the most appropriate no observed adverse effects level (NOAEL) or lowest observed adverse effects level (LOAEL) and (2) apply the relevant uncertainty and modifying factors (as with exposure limit estimating for developmental toxicity).

1. Identify the Most Appropriate NOAEL or LOAEL

The hierarchy for selection of a study described for developmental toxicity (Section 2.3.2.3) is also appropriate for use in identifying appropriate chronic toxicity studies. In addition to the criteria listed, a chronic (lifetime) study is preferable to a subchronic study (an acute study cannot be used to quantify risks associated with chronic exposure). It is important that exposure occurs over a significant portion of the experimental subject's life to parallel a lifetime exposure of the human population. Issues related to the quality of the study should also be considered in selecting the most appropriate studies. Additional information on selection criteria can be reviewed in the IRIS documentation file (IRIS, 1997).

2. Apply Relevant Uncertainty and Modifying Factors

The calculations for chronic systemic toxicity use the modifying and uncertainty factors listed for developmental toxicity (see Table 2-1). In addition, an uncertainty factor may be used when a chronic study is not available and a subchronic (e.g., 90-day) study is used. This is generally a tenfold factor (Abernathy and Roberts, 1994; IRIS, 1997). The product of all uncertainty/modifying factors may range widely depending on the toxicity database. If a chronic human epidemiologic study is available, the uncertainty factor may be as small as 1. However, uncertainty factors of 10,000 may be appropriate (Bolger et al., 1990; U.S. EPA, 1990b).

While uncertainty factors address specific concerns, the modifying factor covers a wider range of circumstances. A common modifying factor adjustment results from differences in absorption rates between the study species and humans,

differences in tolerance to a chemical, or lack of sensitive endpoint. The default value for a modifying factor is 1, but may range up to 10 (see Table 2-1).

The uncertainty factor that deals with data gaps is relatively new (Abernathy and Roberts, 1994). It has been developed because the dose-response data often address a limited number of effects and may not adequately address effects of major concern. In some cases there are a number of studies, but the focus of analysis is narrow and not sufficiently sensitive. In other cases, there is not a sufficient number or breadth of studies. Other reasons for applying a modifying factor are discussed in the specific developmental toxicity guidance (U.S. EPA, 1991a); these include data on pharmacokinetics or other considerations that may alter the level of confidence in the data. EPA has used the criteria that the following studies be available for a high level of confidence in an RfD:

Table 2-1. Uncertainty Factors and Modifying Factors for Estimating Exposure Limits for Developmental Effects

Uncertainty or Modifying Factor	General Comments	Standard Value
Uncertainty factor: human (intraspecies)	Used to account for the variability of response in human populations.	10
Uncertainty factor: animal to human (interspecies)	Used to account for differences in responses between animal study species and humans.	10
Uncertainty factor: data gaps	Used to account for the inability of any study to consider all toxic endpoints. The intermediate factor of 3 (1/2 log unit) is often used when there is a single data gap exclusive of chronic data (see IRIS, 1997).	3 to 10
Uncertainty factor: LOAEL to NOAEL	Employed when a LOAEL instead of a NOAEL is used as the basis for calculating an exposure limit. For "minimal" LOAELs, an intermediate factor of 3 may be used.	3 to 10
Modifying factor	Has been used for differences in absorption rates, tolerance to a chemical, or lack of sensitive endpoint. The default value is 1.	1 to 10

LOAEL = Lowest observed adverse effects level.
NOAEL = No observed adverse effects level.
Source: Adapted from Abernathy and Roberts (1994). Their work also cites: Abernathy et al. (1993); Barnes and Dourson (1988); IRIS (1997); and Jarabek et al. (1993).

> . . . two adequate mammalian chronic toxicity studies in different species, one adequate mammalian 2-generation reproductive toxicity study, and two adequate mammalian developmental toxicity studies in different species (Dourson et al.,1992; U.S. EPA, 1989c).

The same type of concern regarding the completeness of a database is reflected throughout the ATSDR Toxicological Profiles. For example, the profiles do not provide an MRL for chemicals that have NOAELs and only LOAELs resulting in severe effects.

The uncertainty and modifying factors are divided into the NOAEL or LOAEL to obtain an estimated dose using the following equation:

$$\text{RfD} \quad \frac{\text{NOAEL or LOAEL}}{\text{UF} \quad \text{MF}} \qquad (2\text{-}1)$$

where

RfD	=	RfD or exposure limit for the target analyte
NOAEL or LOAEL	=	NOAEL from the selected study
UF	=	multiplicative product of uncertainty factors
MF	=	modifying factor.

This value is analogous to EPA's RfD. If an alternative exposure limit is calculated, the results, in milligrams per kilogram per day, can be used in Equations 3.3 and 3.2, which are discussed in Section 3, to calculate fish meal consumption limits.

As a point of reference, EPA has estimated that the RfDs they develop have an uncertainty spanning approximately 1 order of magnitude (U.S. EPA, 1987a). As discussed previously, it is necessary to fully characterize the uncertainties and assumptions that are incorporated in fish consumption limits. A description of the variability in dose-response results and their impact on fish consumption limits, descriptions of the data gaps, study limitations, and assumptions are also important in providing a context for fish consumption limits based on developmental toxicity or other types of toxic effects. It may be useful to review the description of uncertainties and assumptions associated with dose-response evaluations provided in Sections 2.3.5 and 5.1.1.12. If this document is the only source consulted for dose-response data, note that the literature review conducted for the development of these values was limited to secondary sources such as ATSDR Toxicological Profiles, IRIS, HDSB, and standard toxicological texts (all are cited in the individual chemical discussions). The list of study characteristics provided in Section 2.3.2.3 may be useful for identifying data gaps and sources of uncertainty. The inclusion of this type of information in the risk management process that follows risk assessment, will provide a better overall understanding of the limitations and uncertainties inherent in the fish consumption limits.

2.3.2.3 Developmental Toxicity—

Developmental toxicity has been a recognized medical concern, research subject, and impetus for restricting exposures of pregnant women to developmental contaminants for several decades. However, it is not as well studied as other health effects such as cancer, and significant gaps in our understanding of causality and appropriate protective measures remain. Developmental toxicity incorporates a wide range of effects involving all organ systems in the body. Prenatal and lactational exposure involves indirect exposure of the developing fetus; the effective dose may vary with the period of exposure and the specific chemical. In the past two decades, researchers have determined that the hypothetical maternal barrier, in the past thought to provide protection for the fetus during the prenatal period, does not effectively exist. In fact, prenatal exposure may be especially risky due to the rapid cell replication and differentiation that occurs in the fetus prior to birth. These same processes also occur at elevated rates in children and adolescents, causing them to be more susceptible to some chemical-induced toxicity than adults. Chemical exposures that cause alterations in the cell replication and developmental processes can lead to serious birth defects, miscarriages, stillbirths, developmental delays, and a variety of other adverse effects. A large number of toxic chemicals that have been tested in recent years have demonstrated developmental toxicity in animal test systems. Consequently, the exposure of pregnant women to toxic chemicals has become an area of considerable concern.

Many developmental effects may have environmental causes; however, it is difficult to establish a causal link in epidemiological studies due to confounders that arise from the variability in human exposure. It has been estimated that 20 percent of the developmental defects observed in children are due to genetic causes, 10 percent to known factors, and 70 percent to unknown factors (U.S. EPA, 1991a); some portion of the 70 percent may be attributable to environmental exposures.

EPA has studied issues in developmental toxicity and risk assessment for developmental toxicants over the past two decades and has developed guidance for evaluating developmental toxicants and establishing health-based exposure limits. The initial guidance for risk assessment of developmental toxicants was provided in 1986 (U.S. EPA, 1986e) and has been refined in the current *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a). The recommended approach uses a NOAEL to calculate an RfD in a manner similar to that used for the calculation of an RfD based on chronic exposure toxicity. EPA is also considering use of a benchmark dose approach for developmental toxicants under some circumstances; consequently, the guidelines may be amended in the future (U.S. EPA, 1991a). The methodology described in this guidance document follows the current EPA recommendations. The reader is referred to this and other sources cited throughout this section for further information on developmental toxicity risk and risk assessment.

EPA is working to incorporate new data on developmental and other types of toxicity into the RfDs. The reader can use the information provided on individual

target analytes (in Section 5) and the methodology discussed in this section to calculate exposure limits based on their evaluation of the toxicological literature. Section 5 identifies specific developmental outcomes and the associated dose-response data (i.e., LOAELs or NOAELs) that can be used to carry out the calculations. The reader may also wish to conduct a data search to identify any recent data on the chemicals of major interest in their areas.

Several chemicals, including lead, PCBs, methylmercury, and some pharmaceuticals, are known to cause developmental toxicity in humans. This information comes from large-scale poisoning incidents that resulted in serious developmental effects in a large number of offspring. Human dose-response studies cannot be carried out with planned dosing for developmental toxicants. However, developmental toxicity studies have been carried out on many environmental contaminants in animals. Many of these have yielded positive results (U.S. EPA, 1991a). It is difficult to specifically interpret the dose-response relationship between effects in animal studies and anticipated observable effects in the human population. Research has been conducted to evaluate the relationship between known human developmental toxicants and animal testing results; many similarities in response were found. Alternatively, chemicals that caused developmental effects in animals were studied for effects in humans. These evaluations have yielded mixed results. It has been theorized that the lack of concurrence in results may be due in part to the limited nature of the human data differences in exposure route and the timing and duration of exposure (U.S. EPA, 1992e). Further analysis has indicated that:

> The minimally effective dose for the most sensitive animal species was generally higher than that for humans usually within 10-fold of the human effective dose, but sometimes was 100 times or more higher (U.S. EPA, 1991a).

The Guidelines go on to state that:

> Thus, the experimental animal data were generally predictive of adverse developmental effects in humans, but in some cases, the administered dose or exposure level required to achieve these adverse effects was much higher than the effective dose in humans. (U.S. EPA, 1991a)

A number of assumptions are made in approaching developmental toxicity risk assessment in the absence of specific information:

- Adverse effects in experimental animals may pose a hazard to humans.
- The four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) are all of concern, rather than only malformations and death, which were the primary effects considered in the past.

- The type of developmental effects seen in animals is **not** necessarily the same as that produced in humans.
- The most appropriate species is used to estimate human risk when data are available (e.g., pharmacokinetic). In the absence of such data, the most sensitive species is used.
- A threshold is assumed based on the capacity of the developing organism to repair or compensate for some amount of damage (U.S. EPA, 1991a).

Although it is assumed there is a threshold for developmental toxicity, EPA has stated that:

> . . . a threshold for a population of individuals may or may not exist because of other endogenous or exogenous factors that may increase the sensitivity of some individuals in the population (U.S. EPA, 1991a).

The Agency is currently sponsoring research to better characterize the dose-response relationship for developmental toxicants. This includes an evaluation of the threshold concept (U.S. EPA, 1991a). The process of risk assessment, as recommended in the 1991 EPA guidelines, generally follows the four-step process described in this document. However, hazard identification and dose-response evaluation are combined in the developmental toxicity guidelines because "the determination of hazard is often dependent on whether a dose-response relationship is present" (U.S. EPA, 1991a).

Definitions

There is no one consistent definition of developmental toxicity (U.S. EPA, 1986e). Developmental toxicity may include the range of effects from early pregnancy loss to cognitive disorders detectable only long after birth. The severity of developmental effects ranges from minor alterations in enzyme levels, with no known associated pathology, to death. Developmental toxicity also encompasses health endpoints having genetic and nongenetic bases. EPA's 1986 guidelines (U.S. EPA, 1986b) provide useful definitions that are used in this document to classify different types of developmental effects and to define the scope of effects included under the overall heading of developmental effects.

- **Developmental Toxicology**—The study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth (defined below), and (4) functional deficiency.

- **Functional Developmental Toxicology**—The study of alterations or delays in the physiological and/or biochemical functioning of the individual during critical pre- or postnatal development periods.

- **Embryotoxicity and Fetotoxicity**—Any toxic effect on the conceptus as a result of prenatal exposure. The distinguishing feature between the two terms is the stage of development during which the injury occurs (the embryonic stage lasts until approximately 8 weeks postconception followed by the fetal stage). The terms include malformations and variations, altered growth, and in utero death.

- **Altered Growth**—An alteration in offspring organ or body weight or size. These alterations may or may not be accompanied by a change in crown-rump length and/or in skeletal ossification. Altered growth can be induced at any stage of development and may be reversible or may result in a permanent change.

- **Malformations**—Permanent structural changes that may adversely affect survival, development, or function. The term teratogenicity is used to describe only structural abnormalities.

- **Variations**—Divergences beyond the usual range of structural constitution that may not adversely affect survival or health. Distinguishing between variations and malformations is difficult because responses form a continuum from normal to extremely deviant. (U.S. EPA, 1986b, 1991a).

Other terminology is often used (e.g., anomalies, deformations, and aberrations) but definitions may vary.

For purposes of this guidance document, the definition of developmental toxicology given above will be used to describe the range of effects considered in this section. This provides a broad scope for evaluation of developmental effects, including those resulting from both prenatal and preconception exposures and effects that are observable pre- and postnatally. This section does **not** include a discussion of reproductive system effects (i.e., damage to the reproductive system), such as sterility, that result from exposure **during** adulthood and that may prevent conception from occurring but that do not effect the development of another individual. This type of toxicity is included under the Chronic Toxicity heading in each profile in Section 5.

Carcinogenic effects occurring prior to adulthood may be considered developmental effects under some circumstances. These can be evaluated using the methods described in the previous section on carcinogenicity in keeping with EPA recommendations (U.S. EPA, 1986e) and, similarly, mutagenic effects can be evaluated using criteria discussed in *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), as described in Appendix B.

Special Issues in Evaluating Developmental Toxicants

Studies of developmental toxicants that are most useful in quantitative risk assessment include human epidemiological studies and animal toxicology studies. Epidemiological studies have been conducted on very few chemicals. Animal studies, which are more readily available, pose problems related to interspecies extrapolation (see statements in Sections 2.3.5 and 5 regarding uncertainty). The *Guidelines for the Health Assessment of Suspect Developmental Toxicants* (U.S. EPA, 1991a) provides guidance on evaluating various types of developmental toxicity studies.

Some aspects of the evaluation of developmental toxicity studies differ from the approaches and data that would be sought from most other types of toxicity studies. One area of concern is the need to ascertain overall reproductive performance, not only adverse effects on developing individuals. Exposure to a toxicant often results in developmental damage at a very early stage of growth. This may prevent implantation or lead to very early fetal loss. Such losses are usually only detectable in animal studies by comparing the number of individuals per litter or the number of litters produced to the same outcomes in control populations. Very early losses are often absorbed and are not identifiable via other means. In human studies such losses are not usually identified, although prospective studies have used the monitoring of pregnancy markers, such as human chorionic gonadotropic (HCG) hormone, to identify very early post-implantation pregnancy losses (see EPA, 1991a for further discussion).

Another area of concern in developmental toxicity studies that is not usually of significant interest in other types of toxicity studies is the importance of weight changes. According to the Federal guidelines, “A change in offspring body weight is a sensitive indicator of developmental toxicity . . .” (U.S. EPA, 1986e). A relatively small weight change is not generally considered important in toxicological studies of adult subjects; however, this is considered an important effect during development. For example, the human corollary to decreased weight in animals may be low birth weight, although this cannot be directly implied from animal studies. Low birth weight in infants is a significant and often serious public health problem. Weight gain or loss may also be organ-specific and may be indicative of organ toxicity. For example, decreased brain weight may be indicative of retarded or neurological development.

An issue that is often raised in developmental toxicity studies is maternal toxicity. Although some researchers have suggested that the presence of maternal toxicity undermines the validity of results observed in offspring, some level of maternal toxicity should be observed in this type of study at the high end of the dose regimen (U.S. EPA, 1986e). The EPA health assessment guidelines describe appropriate endpoints of maternal toxicity. One reason that identification of maternal toxicity is an important component of a developmental toxicity study is that it can provide information on the likelihood of developing individuals being more or less susceptible than adults to an agent. Agents that produce developmental toxicity in offspring at doses that do not cause maternal toxicity are

of greatest concern because these dynamics suggest that developing individuals are more sensitive or selectively affected (U.S. EPA, 1986e). Those that produce effects in parent and offspring at the same dose are also of concern; it should not be assumed that offspring toxicity results from maternal toxicity because both may be sensitive to the given dose level (U.S. EPA, 1986e).

Methods for Estimating Exposure Limits

This section was not designed to provide detailed guidance on conducting dose-response evaluations. Rather, it provides a more detailed discussion of the EPA method to calculate RfDs, which is presented in Section 2.3.2.2. This method can be used by the reader to estimate exposure limits for developmental effects as necessary. As previously discussed, the major steps are identification of the most appropriate NOAEL or LOAEL and application of relevant uncertainty factors and modifying factors.* This discussion assumes a familiarity with basic concepts in epidemiology, toxicology, and human biology. Guidance is also provided in the discussions of individual target analytes (Section 5.3) on selection of a sensitive health endpoint or study and use of uncertainty and modifying factors.

1. Identify Most Appropriate NOAEL or LOAEL

The approach discussed in this section uses NOAELs and LOAELs in a manner analogous to that used for the development of chronic toxicity RfDs. The EPA guidance on developmental toxicity (U.S. EPA, 1991a) also discusses the use of a benchmark dose to evaluate toxicity. This approach employs a different method of evaluation than that previously described under chronic exposure in Section 2.3.2.2. The benchmark approach uses the response rate as a critical factor (e.g., the dose effective in 10 percent of the study subjects). Such an approach requires more extensive information than is available for most target analytes. It is recommended that the reader review the 1991 guidance on developmental toxicity risk assessment, which provides extensive specific guidance on the evaluation and selection of various types of developmental toxicity studies (U.S. EPA, 1991a). The 1991 guidelines provide a scheme for categorization of health-related data, which includes descriptions of sufficient evidence and insufficient evidence for dose-response evaluations. The guidelines recommend that a dose-response evaluation not be conducted unless there is sufficient evidence. To evaluate developmental toxicity, data from human studies may be used. However, for most chemicals, human study data are not available and toxicity studies in animals are used (U.S. EPA, 1987a, 1991a). EPA's Office of Health Effects Assessment (OHEA) may also be consulted for guidance on obtaining additional information and identifying existing databases on developmental toxicants.

* Characterization of the database is also an important step. However, it is assumed in this document that an abbreviated approach will be taken to estimating exposure limits. If the summary data provided in this work or taken from other sources are used, it will not be possible to fully characterize and categorize the database. (See U.S. EPA, 1991a, pp. 63816-63817.)

Exposure limits may be estimated using the NOAEL or LOAEL obtained from toxicological studies of animals and humans or epidemiological studies of humans. The NOAEL, usually expressed in mg dose per kg body weight of the subject per day, is the highest dosage given to the animals over their lifetime that results in no observable adverse effects. When a NOAEL is not available, the lowest dose at which an adverse effect was observed is used. Often there are several NOAELS and LOAELs for a chemical; selection of the most appropriate value is a judgment based on the quality of the studies, sensitivity of the health endpoint and test species, and numerous other factors. The following hierarchy may be useful in selecting a study from which to use a NOAEL or LOAEL:

- A human study is preferable to an animal study. When a human study is unavailable, an animal study is selected that uses a species most relevant to humans based on the most defensible biological rationale (e.g., pharmacokinetic data).
- In the absence of a clearly most relevant species, using the most sensitive species for the toxic effect of concern is preferable (e.g., exhibiting a toxic effect at the lowest dose).
- A study with the appropriate exposure route(s) is preferable, oral or gavage is appropriate for oral exposure.
- A study with sufficient subjects to obtain statistical significance at relatively low exposure levels is required.
- A recent study identifying adequately sensitive endpoints is preferred (e.g., not mortality).
- An adequate control population is required.
- In general, a NOAEL is preferable to a LOAEL. When a NOAEL is unavailable, the LOAEL that generates the lowest exposure threshold (after the application of uncertainty and modifying factors) is usually selected.

It is necessary to consider overall study quality and study design in selecting the most appropriate study or studies. The reader should refer to the 1991 *Guidelines for Developmental Toxicity Risk Assessment* for further details (U.S. EPA, 1991a).

2. Apply Relevant Uncertainty and Modifying Factors

Once a LOAEL or NOAEL is selected, the value obtained (in mg/kg/d) is divided by factors to account for the various types of uncertainty inherent in estimating a threshold for developmental effects. These factors, referred to by EPA as uncertainty factors and modifying factors, are summarized in Table 2-1, which was adapted from a discussion of RfD development in Abernathy and Roberts (1994). Many developmental toxicity studies use a brief dosing period during gestation (although use of a study with a single dose is not recommended). An uncertainty factor is usually not added for the short duration of the study under these circumstances. This differs from the calculation of exposure limits based on chronic

exposure toxicity (discussed previously in this section) when an uncertainty factor is typically applied for the use of a less-than-lifetime study.

The total product of all of the uncertainty and modifying factors may range widely depending on the types of studies available. If a chronic human epidemiologic study is available, the uncertainty factor may be as small as 1. However, uncertainty factors of 10,000 have been used (IRIS, 1997). While the uncertainty factors address specific concerns, the modifying factors cover a wider range of circumstances. A common modifying factor adjustment results from differences in absorption rates between the study species and humans, differences in tolerance to a chemical, or lack of a sensitive endpoint. The default value for a modifying factor is 1. The uncertainty factor that deals with data gaps is relatively new (Abernathy and Roberts, 1994). It has been developed because the dose-response data often address a limited number of effects and do not adequately address effects of major concern. In some cases there are a number of studies, but the focus of analysis is narrow and insufficiently sensitive. In other cases, there is not a sufficient number or breadth of studies (see Dourson et al., 1992, for experimental support of this database factor). Other reasons for applying a modifying factor are discussed in the specific developmental toxicity guidance (U.S. EPA, 1991a); these include data on pharmacokinetics or other considerations that may alter the level of confidence in the data.

The uncertainty and modifying factors are divided into the NOAEL or LOAEL to obtain an RfD using Equation 2-1 (Section 2.3.2.2). If an exposure limit is calculated for developmental toxicity, the results, in mg/kg/d, can be used in Equations 3-3 and 3-2 discussed in Section 3, to calculate fish consumption limits. Examples of how this is carried out are provided in Section 3.

As discussed above, it is necessary to have a full characterization of the uncertainties and assumptions incorporated in fish consumption limits. Assumptions and uncertainties associated with dose-response assessment are discussed in Sections 2.3.5 and 5.1.1.12. As a point of reference, EPA has estimated that the RfDs that they develop have an uncertainty spanning approximately 1 order of magnitude (U.S. EPA, 1987a). A description of the variability in dose-response results and their impact on fish consumption limits and descriptions of the data gaps, study limitations, and assumptions are also important in providing a context for fish consumption limits based on developmental toxicity or other types of toxic effects. It may be useful to review the description of uncertainties and assumptions associated with dose-response evaluations provided in Section 2.3.5 to identify major sources of uncertainty. In addition, the list of study characteristics provided previously in this section may be useful for identifying data gaps and sources of uncertainty. If this document is the only source consulted for dose-response data, it should be noted that the literature review conducted for the development of values was limited to secondary sources such as ATSDR Toxicological Profiles, IRIS, HDSB, and standard toxicological texts (all are cited in the individual toxicological profile summaries). The inclusion of this type of information in the risk management process following risk assessment will provide a better overall

understanding of the limitations and uncertainties inherent in the fish consumption limits.

The 1991 developmental toxicity risk assessment guidelines provide a scheme for categorization of health-related data, including descriptions of sufficient and insufficient evidence for dose-response evaluations. The guidelines recommend that a dose-response evaluation not be conducted unless there is sufficient evidence (U.S. EPA, 1987a, 1991a). The reader is referred to this source for additional information on all aspects of risk assessment for developmental toxicity.

EXAMPLE

The chemical group polychlorinated biphenyls (PCBs) was chosen as an example of how an estimated exposure limit for developmental effects can be developed for target analytes.

It is advisable to conduct a thorough literature search to identify all relevant studies. The summaries of dose-response and other toxicity data provided in Section 5 provide an overview; however, it is advisable to seek additional data, including any newly released information, whenever practical. An abbreviated approach to estimating an exposure limit, using the information provided in this guide, is discussed below.

In addition to the data in Section 5 specifically discussing developmental toxicity, it is useful to review other relevant data. This includes chronic toxicity and carcinogenicity, including especially reproductive system toxicity and other organ toxicities that are similar to, or affect the same system as, that observed in developmental toxicity studies. All other sections of the target analyte toxicological profile summary may also have a bearing on understanding and interpreting the results of developmental toxicity studies. They may support or refute the results observed or point out potential data gaps (e.g., organ toxicities observed in numerous studies of adult animals but not evaluated in developmental toxicity studies).

It is especially necessary to review any discussions of reproductive system toxicity in the Chronic Toxicity section of a target analyte discussion. This may have a bearing on the interpretation of developmental toxicity study results. For example, alteration in hormonal balances, structural changes in the reproductive system, and other adverse effects may modify the ability to maintain pregnancy. This could lead to a reduction in the number or size of litters or other impact on pregnancy outcome. These factors would need to be considered when reviewing developmental toxicity studies that identify effects such as increased fetal resorptions, fetal death, reduced litter size, and related effects because these effects could arise from damage to the mother rather than the offspring.

(continued)

EXAMPLE (continued)

There are numerous other effects on reproductive toxicity that may affect interpretation of developmental toxicity study results. The reader may wish to consult texts on this subject for further information. See the relevant reproductive system toxicity discussion for PCBs in Section 5.7.

It may also be helpful to survey the available information on related chemicals (e.g., structural relatives of PCB would include organochlorine pesticides). This may provide general information on effects that are common to several or all members of a chemical group. Such findings lend support to conclusions regarding toxicity. In addition, studies on related chemicals may have explored effects anticipated (based on adult studies in the chemical of concern) in developing individuals but not evaluated in developmental studies on the chemical of concern. This provides useful information for qualitatively evaluating potential toxicity and may point out critical data gaps.

For Aroclor 1016, the RfD is based on developmental effects seen in monkeys. A NOAEL of 0.001 mg/kg/d was established and an uncertainty factor of 100 was applied (3 for sensitive individuals, 3 for interspecies extrapolation, 3 for database limitations, and 3 for extrapolation from subchronic to chronic). This results in an RfD of 7×10^{-5} mg/kg/d

$$\text{Estimated Exposure Limit} = \frac{0.007 \text{ mg/kg/d}}{100} = 7 \times 10^{-5} \text{ mg/kg/d} \qquad (2\text{-}2)$$

where

0.007 = NOAEL from the selected study
100 = uncertainty factor

A discussion of uncertainty, assumptions, and data gaps should be a part of information supporting an estimated exposure limit. This information can include a summary of the various sources of uncertainty described in Sections 2.3.5 and 5 of this document, information included in the target analyte discussion, and any other information the reader feels would be useful in characterizing uncertainty.

(continued)

EXAMPLE (continued)

The discussion of data gaps in Section 5.7 includes a list of the types of studies needed based on an interagency review of the available data. Most major categories of uncertainty are covered by this list of studies. The reader may wish to elaborate on why certain studies are needed (e.g., pharmacokinetic studies to generate better information on bioaccumulation, body burden, accumulation in breast milk).

Sources of Additional Information on Developmental Toxicity

The primary source the reader is referred to for additional information on conducting risk assessment for developmental toxicity is: *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a). In addition, there are 165 citations listed in the Guidelines that cover a broad spectrum of literature on developmental toxicity and risk assessment. The reader may wish to consult these sources for additional guidance on this topic.

2.3.3 Mutagenicity/Genotoxicity

Mutagenicity and genotoxicity data are not generally used to develop risk estimates by themselves, although they are frequently used in conjunction with other information to evaluate other toxicity endpoints (e.g., cancer). There is a wide variety of assays designed to assess the mutagenicity of chemicals; however, there is a limited amount of mutagenicity dose-response data that can be used in quantitative risk assessment. The majority of data involve in vitro test systems, which can provide only qualitative evidence of mutagenicity.

The evaluation of weight-of-evidence (WOE) for carcinogenicity, carried out by EPA for all chemicals having a cancer classification, includes an evaluation of mutagenicity data. Information on genetic toxicity also needs to be considered when developing risk values for developmental and reproductive system effects. Mutagenicity data are summarized in the toxicological profile summaries in Section 5. Readers are urged to consider this information in reviewing the toxicity of target analytes. Because information is less readily available on genetic toxicity and mutagenicity than on other types of risk assessment, and because this type of toxicity is relevant to evaluating developmental toxicity, a brief summary of the current EPA guidelines on these types of toxicity has been included in Appendix B.

2.3.4 Multiple Chemical Exposures: Interactive Effects

Most humans are simultaneously exposed to a number of environmental contaminants. Risk evaluations, however, typically proceed on a chemical-by-chemical basis. Similarly, the development of risk-based exposure guidelines typically focuses on the effects of exposure to chemicals individually rather than

as a group. In many cases, the individual exposures and/or risks are then summed to estimate risks or safe exposure levels for a group of chemicals.

EPA provides guidance on chemical mixtures in risk assessments in *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986d). The guidelines advise the use of the additive approach when data are available only on individual mixture components. Section 3 provides a method for calculating exposure limits for multiple chemical occurrence in single or multiple fish species. The approach is recommended for use when chemicals have the same health endpoints and mechanisms of action. Similarities in the toxicity characteristics of organochlorinated pesticides and organophosphate pesticides are discussed in Appendix C. It does not address chemicals with dissimilar actions.

The 1986 Guidelines also address circumstances when data are available on antagonistic or synergistic interactions. They state that "information must be assessed in terms of both its relevance to subchronic or chronic hazard and its suitability for quantitatively altering the risk assessment." These two criteria are essential for selection of interactive data applicable to quantitative risk assessment. However, the criteria preclude the use of most interactive data in risk assessments of long-term exposures because many interactive studies focus on short-term exposure. An additional complication is introduced to this type of analysis for mixtures containing more than two chemicals. For those groups, it is necessary to ascertain whether the presence of additional chemicals in the mixture will alter any known interactions between any two chemicals having interactive data (U.S. EPA, 1986d).

The type of information that is often available (acute effects interactions and mechanisms of action) is not readily applicable to the quantitative assessment of chronic health risks of multiple chemical exposures (U.S. EPA, 1986d). The guidelines recommend that this type of information be discussed in relation to its relevance to long-term health risks and interactive effects without making quantitative alterations in the risk assessment. Much of the interactive information included in the toxicological profiles in Section 5 was obtained from the ATSDR Toxicological Profiles for various chemicals. Readers are encouraged to consult these ATSDR documents if they require interactive data.

The information obtained from ATSDR and/or that may be implied from the toxicological nature of many of the target analytes is related to the chemical's interaction with basic processes, such as metabolism. When these functions are altered (e.g., by the induction of microsomal enzymes), the metabolism of other endogenous or exogenous chemicals may be altered. This is particularly problematic for individuals using pharmaceutical drugs to address medical conditions. As the PCB discussion in Section 5.7 notes, alteration in metabolism of medications may require adjustment of dosages. This is not a hypothetical problem; exposure to various chemicals has reportedly resulted in altered response to medications. Information regarding these types of effects are discussed in Section 5 for the target analytes.

EPA has recently developed a database to disseminate available information on interactive effects of chemical mixtures. This database, called MIXTOX, contains summaries of information from primary studies in the open literature on binary mixtures of environmental chemicals and pharmaceutical chemicals. Data provided include the duration of the study, animal species, dose ranges, site, effects, and interactions. Available MIXTOX information on the target analytes is presented in Section 5. The majority of data obtained through MIXTOX consisted of the results of acute studies. Many studies indicated additive effects. Other types of interactions (e.g., inhibition, synergism) were usually not provided. The relevance of this information to specific waterbodies will depend on the chemical mixtures that are known to occur, based on fish sampling results. **In the absence of quantitative information on interactive effects, these guidelines suggest the use of an additive approach to evaluation of chemical mixtures for carcinogens and for noncarcinogens that are associated with the same adverse health endpoints.** The equation used in this approach is presented and discussed in Section 3.5.

2.3.5 Assumptions and Uncertainties

Numerous assumptions are required to develop risk values from dose-response data. Uncertainties arise from the assumptions, from the nature of the dose-response data, and from our imperfect understanding of human and animal physiology and toxicology. Depending on the quality of the studies, there may also be uncertainty regarding the nature and magnitude of the effects observed in toxicological and epidemiological studies. However, evaluation of study quality is a complex process and involves such diverse topics as animal housing conditions and pathological evaluations. Often there is not sufficient information provided in study summaries (either in a journal article or report) to fully evaluate the quality of the study and the assumption must be made that good laboratory practices and scientific methods were followed.

Major assumptions that are used in the evaluation of dose-response data are discussed at length in the EPA risk assessment guidance documents on specific toxicities (e.g., for carcinogenicity, numerous assumptions are discussed including the selection of the dose-response model, use of benign tumors in estimating response, use of the upper bound estimate of the slope, and use of surface area instead of body weight to adjust dose [EPA, 1986a,c,e; 1996d]).

A critical assumption underlying all animal-human extrapolations is that there is a relationship between toxicity in test animals and the toxicity anticipated in humans. There can be significant differences in metabolism and other physiological aspects of study animals and the human population (e.g., absorption, metabolism, and excretion). Although many of these aspects are well-characterized, the relationship between interspecies differences and the toxicity of specific chemicals is usually not known. There is also uncertainty regarding the appropriateness of the test species for evaluation of a chemical's effects on humans. Generally, the species of animal that most closely resembles humans in response to the toxicity of a particular chemical is used in the risk assessment. When such information is not

available (as is often the case), the species of animal that is most sensitive to a particular effect is used in the evaluation of that effect for a chemical. Although the existence of a relationship between animal and human toxicity is acknowledged by most scientists, there is not universal consensus on the nature of the relationship for many chemicals and endpoints (e.g., male rat kidney toxicity associated with α-2-globulin may not be applicable to humans).

A second critical assumption is the existence of a threshold for most non-carcinogens and no threshold for carcinogens. The threshold issue is under evaluation for many chemicals and endpoints (e.g., epigenetic [nongenetic] carcinogens, developmental effects). Issues of this type will be resolved as more information becomes available on the basic mechanisms of toxicity and actions of specific chemicals. Future revisions of this document will provide additional guidance as it becomes available.

Additional uncertainty regarding dose rate and the duration of exposure is generated by the use of test animals. Many animal studies are conducted for the lifetime of the animals; however, the human lifetime is significantly longer than the 2-year study period of the usual experimental subjects (e.g., rats or mice), which may impact bioaccumulation and toxicity. When human studies are used as the basis for risk estimates, they are usually of occupationally exposed individuals, who were exposed intermittently during adulthood over two to three decades rather than continuously exposed over a lifetime. Often they are not followed into old age, when many effects become clinically detectable. In addition, human exposures are often confounded by concurrent exposure to other chemicals. Consequently, the use of human studies also introduces numerous uncertainties to the toxicity evaluation process.

Various assumptions are made in most risk assessments regarding the use of numeric adjustments for extrapolation of study results from animals or human studies to the general population. The extrapolation models used to estimate individual or population risks from animal or human studies introduce “margins of safety” to account for some aspects of uncertainty. These models are designed to provide an upper bound on cancer risk values and a conservative RfD for noncarcinogens. Uncertainties arise from the application of uncertainty and modifying factors in the calculation of RfDs. These factors are based on the best available scientific information and are designed to provide a safe margin between observed toxicity and potential toxicity in a sensitive human. The RfD is considered to be an estimate with uncertainty spanning approximately 1 order of magnitude. EPA considers the RfD to be a reference point to be used in estimating whether adverse effects will occur (IRIS, 1997). The IRIS Background Documentation has provided additional insight into the uncertainty inherent in RfDs:

> Usually doses less than the RfD are not likely to be associated with adverse health risks, and are, therefore, less likely to be of regulatory concern. As the frequency and/or magnitude of exposures exceeding the RfD increase, the probability of adverse effects in a human population increases. However, it should not be

> categorically concluded that all doses below the RfD are "acceptable" (or will be risk-free) and that all doses in excess of the RfD are "unacceptable" (or will result in adverse effects) (IRIS, 1997).

For carcinogens, the upper 95 percent confidence bound on the linear component of the linearized multistage model is currently used in estimating a cancer potency to introduce a safety margin. It is assumed that this provides a plausible upper bound estimate of potency in the human population (U.S. EPA, 1986a). EPA's new cancer guidelines (which have not been finalized as of this writing) propose using straight line extrapolation (U.S. EPA, 1996d).

Many numerical assumptions related to anatomy and physiology are used in calculating risk values (e.g., average adult body weight of 70 kg, animal dietary consumption estimates). The application of these assumptions depends on the type of data being used. These assumptions are typically based on a substantial amount of information on average or mean values. However, individual variations within the human population generate uncertainty related to the application of the assumptions.

Uncertainty is significantly related to the amount and quality of toxicological and epidemiological data available. There is a greater degree of certainty for chemicals having human epidemiological studies that encompass a variety of population subgroups over a dose range. However, this type of data is not usually available. Uncertainty related to the database is often endpoint-specific. For example, there may be a substantial amount of data regarding carcinogenic effects but little information on developmental toxicity. This is the case for many of the chemical contaminants discussed in Section 5.

Selection criteria for studies are listed for chronic and developmental toxicity in this section. Where the most appropriate types of data are not available (based on these selection criteria) there is usually greater uncertainty regarding the risk values and risk estimates that are calculated. Many of the criteria address the quality of the studies used to estimate dose-response parameters. Weight-of-evidence guidelines, also discussed in this section for specific toxicity types, provide useful insight into the adequacy of the data supporting a risk value.

Bioassays conducted on single cell lines generate greater uncertainty than animal studies due to their isolation from normal physiological processes. However, some types of effects can be studied most efficiently using these tests. Various types of mutagenicity and cellular level assays provide insight into the potential for genetic damage and damage to specific types of cell systems. These data are very difficult to interpret in the context of human risk because the relationship between study results and human effects has not been well-characterized. This type of study is most often used to support other study results (e.g., positive mutagenicity studies support animal studies indicating carcinogenicity).

Certain chemicals have such limited data for one or more toxic effects that toxicity reference values cannot be determined. Some of these chemicals are poorly characterized for all known/suspected toxicity endpoints. For other chemicals, data may be well-characterized for certain toxic effects, but inadequate for others. For instance, the carcinogenicity of organochlorines has been well-characterized in animals and humans, but other toxic endpoints, including systemic effects and reproductive effects, have not been extensively investigated. Limitations for the 25 contaminants in this assessment are described in detail in Section 5.

EPA does not recommend specific factors for modifying toxicity data in cases where these data are so limited that a dose-response relationship cannot be determined. However, as the above examples show, lack of toxicity reference values for a given chemical does not necessarily mean that the chemical causes no effect. Therefore, readers will need to evaluate if the lack of specific kinds of toxicity data affect the adequacy of protection afforded by the consumption limit. For example, if the chemical is a suspected developmental toxicant, but quantitative developmental toxicity data are lacking, readers may determine that a consumption limit based on other health endpoints is not sufficiently protective of women of reproductive age and children.

In summary, uncertainty may be generated by many components of a dose-response evaluation. Some of these are dealt with quantitatively through the application of uncertainty factors, modifying factors, or the use of an upper bound estimate. Others may be referred to qualitatively, through a discussion of data gaps or inferential information (e.g., studies that appear to show greater susceptibility at certain ages). The goal of providing the qualitative information on uncertainty is to give the risk assessor and decision makers sufficient information on the context and support for risk values and estimates so that they can make well-informed decisions.

2.4 EXPOSURE ASSESSMENT

This section is meant to provide readers with a brief overview of EPA exposure assessment methodology. Readers wishing to conduct exposure assessments are advised to read the more detailed documents listed in Appendix A.

Exposure assessment of contaminants in fish involves six components:

- Chemical occurrences in fish
- Geographic distribution of contaminated fish
- Individual exposure assessment
- Population exposure assessment
- Multiple species exposure
- Multiple chemical exposure.

Each of these components is discussed below.

2.4.1 Chemical Occurrences in Fish

Contaminant concentrations vary among different fish species, size classes within a fish species, fish tissues, and contaminants present in ecosystems. Chemical contaminants are not bioaccumulated to the same degree in all fish species. In addition, chemical contaminants are not distributed uniformly in fish tissues; some toxicants bind primarily to lipids and others to proteins. Fatty and/or larger fish often contain higher organic contaminant concentrations than leaner, smaller fish. The correlation between increasing size (age) and contaminant tissue concentration observed for some freshwater fish species (Voiland et al., 1991) may be less evident in estuarine and marine species (U.S. EPA, 1995; Phillips, 1988). Knowing how contaminants differentially concentrate in fish enables risk managers to advise fish consumers on alternative fishing practices (consumption of smaller individuals in a contaminated species) and cooking practices (including skinning, trimming, and cooking procedure) to minimize exposure.

Volume 1 of this series, *Guidance for Assessing Chemical Contamination Data for Use in Fish Advisories, Volume 1: Fish Sampling and Analysis* (U.S. EPA, 1995), provides comprehensive guidance on cost-effective, scientifically sound methods for use in fish contaminant monitoring programs designed to protect public health. It is designed to promote consistency in the data States use to determine the need for fish consumption advisories. By standardizing protocols across regions, risk managers can avoid significant differences in advisories when actual concentrations of chemical contaminants in fish are very similar.

Volume 1 suggests that screening values be compared to annual fish sampling and analysis data to determine where problems may exist. The document also discusses sampling design and field procedures for collecting and analyzing fish and shellfish tissue samples for pollutant contamination. It discusses specific cost-effective analytical methods, quality assurance/quality control (QA/QC) procedures, and identifies certified reference materials and Federal agencies that conduct interlaboratory comparison programs. Procedures for data reporting and analysis that are consistent with the development of the National Fish Tissue Data Repository are also included.

Information on contaminant distributions in different types of fish and fish tissues and across geographical areas is required for a number of reasons. Differential concentrations of contaminants in fish tissues and across fish species affect fish consumer exposures due to differences in individual consumption practices. The geographic origins and modes of transport of chemical contaminants determine the extent and location of these chemicals in fish. Identifying areas of high contamination enables readers to choose initial screening sites and focus limited resources on fisher populations most at risk from consuming contaminated fish.

Many readers will have information on the geographic distribution of contaminants in fish from their fish sampling and analysis programs. Others may need to identify areas of likely contamination. This topic is also discussed in Volume 1. This section briefly reviews likely patterns of chemical distribution based on chemical

properties and other factors. Such geographic information is important in population exposure assessment and for risk communication; readers are encouraged to develop maps showing areas of fish contamination that, combined with demographic information, help target exposed fisher populations for additional risk communication and outreach efforts. Mapping tools available for tracking locational data on fish contaminants, fish advisories, or other related data are discussed in Section 6.

2.4.2 Geographic Distribution of Contaminated Fish

The geographic extent of contamination of fish is an important element in determining the need for further action. These data are also useful in performing population exposure assessments and risk characterization. Two types of information are particularly useful: the locations where contaminated fish have been found, and the sources of potential contamination. The first type of information is provided by fish sampling and analysis programs. When such data are absent, several available sources can help locate sites of possible contamination by the target analytes. Section 2.2.1.2 contains a list of sources of information on potential fish contaminants. Additional information on site selection for fish sampling and analysis programs is provided in Section 6 of Volume 1.

2.4.3 Individual Exposure Assessment

Individual exposure assessments provide descriptions of the overall, media-specific, or site-specific exposure of an individual. These may be normative or high (e.g., highly exposed individual) estimates or be based on actual measurement data.

Individual exposure assessments use essentially the same equation as that used with fish contaminants to calculate fish consumption limits, although they solve for different variables:

$$E_m = \frac{C_m \cdot CR}{BW} \qquad (2\text{-}3)$$

where

E_m = individual exposure to chemical contaminant *m* from ingesting fish (mg/kg/d)
C_m = concentration of chemical contaminant *m* in the edible portion of fish (mg/kg)
CR = mean daily consumption rate of fish (kg/d)
BW = body weight of an individual consumer (kg).

Individual exposure assessments use data on known chemical residues in fish (C_m) and on human consumption patterns (CR/BW) to estimate exposure (E_m) for hypothetical individuals within given populations (see Equation 2-1). Conversely,

the consumption limits described in Section 3 and provided in Section 4 use the data on known chemical residues in fish (C_m) combined with dose-response data (q_1*s and RfDs, which correspond to maximum "safe" exposure) to estimate maximum safe human consumption rates (CR_{lim}/BW; see Equations 3-1 and 3-3). This document uses this equation only to calculate fish consumption limits. Volume 3 of this series provides additional information on estimating individual and population exposures for purposes of generating risk estimates used in risk management decisionmaking. Individual exposure assessment is discussed in this volume for informational purposes only; it is not used directly in developing the fish consumption limit tables. Increased detail is provided where information is shared between individual exposure assessments and consumption limit calculations.

Depending on the geographic region and/or contaminant involved, contaminant concentrations in fish (C_m) are determined by sampling and analysis programs conducted by public health departments, natural resource agencies, environmental protection agencies, FDA, EPA, and/or agricultural departments. The consumption rate (CR) represents the amount of fish an individual in a given population eats in a day and may be estimated through fish consumption surveys. Finally, the daily dose is divided by the consumer body weight (BW) to arrive at individual exposure.

By using information on the number of individuals in each exposure category, risk managers may aggregate exposures determined in individual assessments to derive population exposure assessments. Population exposure assessments can allow readers to focus limited resources on those contaminants or areas that may pose the highest risks to a large number of persons or to particular populations of interest (e.g., subsistence fishers).

Note: The consumption limits described in this document assume that no other exposure to any of the 25 target analytes occurs. However, a potentially significant source of contaminant exposure is the consumption of commercially caught freshwater, estuarine, and marine fish. Consumption limits for noncommercially caught fish may not be sufficiently protective of consumers of both commercially and noncommercially caught fish. It is recommended therefore, that, whenever possible, readers take other significant sources of exposure into account when conducting exposure assessments and/or developing consumption limits.

2.4.3.1 Exposure Variables—

Equation 2-3 uses three parameters to calculate individual exposure (E_m) to fish contaminants from noncommercially caught fish: consumption rate (CR), consumer body weight (BW), and contaminant concentration (C_m). Equations 3-1, 3-2, and 3-3 in Section 3 also use body weight and contaminant concentration and meal size (MS) in developing consumption limits. With the exception of C_m, which is determined through sampling and analysis programs, these parameters are discussed below.

Body Weight

Both consumption limit and exposure assessment calculations require specific body weights (usually in kilograms) for individuals in order to derive the contaminant daily dose in milligrams contaminant per kilogram consumer body weight per day (mg/kg/d). The *Exposure Factors Handbook* (U.S. EPA, 1990a) recommends values for average weights for children and adults, based on the second National Health and Nutrition Examination Survey (NHANES II). Conducted from February 1976 to February 1980, NHANES II surveyed approximately 28,000 noninstitutionalized U.S. civilians aged 6 months to 74 years. The survey oversampled population groups thought to be at risk from malnutrition (low-income individuals, preschool children, and the elderly). Adjusted sampling weights were then calculated for age, sex, and race categories to reflect body weight values for the estimated civilian, noninstitutionalized U.S. population. Although EPA recommends these values for typical Americans, they may not adequately represent some population groups (e.g., Asian-Americans, who are generally smaller in stature and have a lower body weight than the average U.S. citizen). If more accurate data on average body weights of local fisher populations are available, readers are encouraged to use them in place of the default values.

Table 2-2 lists recommended body weight values for adults, women of reproductive age (women from 18 to 45 years of age), and children. These values are derived from data in the *Exposure Factors Handbook* (U.S. EPA, 1990a); the values listed for adults are used directly, while the value for women of reproductive age represents an arithmetic average of three age groups (18-25, 26-35, and 36-45), and the value for children is an arithmetic average of two groups (children <3 and children from 3 to <6). A more protective body weight value for women of reproductive age would be to use the lower 95th percentile body weight of women age 18 to 25 years (Blindauer, 1994). In this document, however, a body weight of 70 kg was used for all adults, including women of reproductive age, to calculate the consumption limits shown in Section 4.

Table 2-2. Mean Body Weights of Children and Adults

Age Group	Mean Body Weight (kg)		
	Males	Females	Males and Females (Averaged)
Adults	78	65	**70**
Women of reproductive age	-	64	-
Children <6	15	14	**14.5**

Source: Adapted from U.S. EPA (1990a).
Bolded values were used in the development of consumption limit tables in Section 4.

Readers are encouraged to use values that average together male and nonpregnant female body weights when assessing exposure to the general adult population. Where consumption rates are known to differ significantly between men and women, however, readers may wish to make gender-specific exposure assessments and use unaveraged gender-specific body weight estimates. When certain developmental toxicants are of concern, readers are encouraged to make separate exposure assessments for children and women of reproductive age.

Meal Size

Meal size is a critical parameter in expressing fish consumption limits, though it is not used directly in calculating exposure (which is expressed in mg/kg/d). Consumption limits expressed in terms of meals per given time period are more understandable than those expressed in kilograms per day. Meal size estimates can also be used to calculate peak acute exposures to fish contaminants (although that information is not used in this document).

Several values for average meal size have been determined through both non-commercial and commercial fish consumption surveys, although these values may not be comparable across studies. For instance, some surveys report meal sizes on the basis of whole, raw fish, while others refer to cooked fillets. Still others do not specify whether the value is based on cooked or raw fish. The average meal size most often cited is 227 g, or 8 oz (Anderson and Amrhein, 1993; Minnesota Department of Health, 1992; Missouri Department of Health, 1992; U.S. EPA, 1995). This meal size corresponds to the value used in the Michigan Anglers Survey, in which individuals were asked to estimate their average meal size compared to a picture showing an 8-oz (227-g) fish meal (West et al., 1989). The same meal size also represents the high-end range used by Dourson and Clark (1990), which is based on the value used in the EPA *Region V Risk Assessment for Dioxin Contaminants* (1988c). A discussion of fish consumption surveys is provided in Appendix D.

EPA has developed meal size estimates for both adults and children under 4. The general adult population includes all adult men and women. Children eat smaller portions than adults, although they may consume significantly more fish per unit body weight. Women of reproductive age were assumed to eat proportionally (per kg body weight) the same amount of fish per meal as other adults.

EPA suggests using a default value of 8 oz (227 g) of cooked fish fillet per 70-kg consumer body weight as an average meal size for both the general adult population and for women of reproductive age for use in exposure assessments and fish advisories if population-specific data are not available. This meal size, however, is not likely to represent higher end exposures, where persons consume more than the average amount in a given meal. These larger meal sizes are important to consider in cases where acute and/or developmental effects from consumption of contaminated fish are of concern.

Meal size can also differ for other population groups and must be scaled accordingly. Children and adolescents, for example, often consume more fish per kilogram body weight than adults. A national food consumption survey conducted by the U.S. Department of Agriculture (USDA) was used to scale the adult meal size value to child meal size values (USDA, 1983). The USDA survey evaluated consumption patterns of approximately 38,000 U.S. citizens over 3-day periods from 1977 to 1978 and is the largest consumption survey of its kind that includes fish. The survey results included meal size data for 10 age groups. Although respondents included both fishers and nonfishers, relative differences reported between the age groups were used to approximate differences in average meal size between different age categories within fisher populations in the current assessment. For children younger than 4 years old, EPA suggests using a default meal size of 3 oz (85 g) if population-specific data are not available. For older children, modifications in consumption limits can be made to tailor limits to their body weights and consumption patterns. The methodology to do so is discussed in Section 3.

Consumption Rate

Although it is necessary to estimate the overall average consumption rate in order to characterize risk, this information is not necessary to provide risk-based consumption limits as in Section 4. Consumption rate information is primarily used to make risk management decisions regarding the allocation of resources and implementation of various public health protection strategies related to consumption of contaminated fish. Consequently, fish consumption patterns and methods for evaluating the resulting risks are presented in a new version of the *Guidelines for Exposure Assessment*, which EPA is currently finalizing. However, due to the significant variability in fish consumption among individuals, readers are urged to conduct their own surveys to determine actual consumption levels when accurate risk estimates are required.

2.4.3.2 Averaging Periods Versus Exposure Durations—

The exposure duration is the time period over which an individual is exposed to one or more contaminants. In the case of an individual fisher, the exposure duration is equivalent to the time interval over which he or she catches and consumes fish. However, fish consumption is frequently not constant over the time period of interest for examining certain health endpoints (e.g., lifetime for chronic effects), particularly for short-term or seasonal recreational fishers. For short-term or seasonal fishers, periods of consumption must be averaged with periods during which no consumption occurs to correspond with the time periods over which chronic health effects are likely to develop. For example, the method usually employed to obtain a lifetime average daily dose is to divide the cumulative dose over an individual's lifetime by the number of days in an average lifetime. For developmental and subchronic effects, the time period over which dose is averaged is much shorter. Consequently, the time periods of concern chosen for use in exposure assessments are called averaging periods.

For pollutants with carcinogenic properties, EPA currently assumes that there is no threshold below which the risk is zero (i.e., for any nonzero exposure, there may be some increase in cancer risk). There is no current methodology for evaluating the difference in cancer risks between consuming a large amount of the carcinogenic contaminant over a short period of time and consuming the same amount over the course of one's lifetime. EPA's current cancer risk assessment guidelines recommend prorating exposure over the lifetime of the exposed individual (U.S. EPA, 1986d) and EPA's proposed cancer guidelines do not address this issue (U.S. EPA, 1996d). To provide usable and easily understood consumption guidance, the unit of 1 month was used as the basis for expressing meal consumption limits for all carcinogenic health endpoint tables shown in Section 4. The limits for carcinogens are based on the assumption that consumption over a lifetime, at the monthly rate provided, would yield a lifetime cancer risk no greater than the acceptable risk listed in each column (i.e., 1 in 10,000, 100,000, and 1 million).

The likelihood of occurrence of noncarcinogenic effects associated with chronic exposure is evaluated through the use of RfDs (as discussed in Section 2.3). Exposure below the RfD is assumed by EPA to be without appreciable risk over a lifetime of exposure. Consequently, the relevant averaging time for both carcinogenic and noncarcinogenic chronic exposure is a lifetime.

As with the carcinogens, the unit of 1 month was used for all tables shown in Section 4 as the basis for expressing meal consumption limits based on chronic systemic health effects and developmental effects. The limits for noncarcinogens are based on the assumption that consumption over a lifetime, at the monthly rate provided, would not generate a health risk. Although consideration was given to inclusion of an acute exposure period (e.g., 1 day), insufficient information on 1-day consumption and acute effects is available to evaluate acute exposure for many of the fish contaminants at this time. It is anticipated that subsequent revisions of this document will more fully characterize acute exposure (see Section 2.3 for a brief discussion).

One or more large meals consumed in a short period (constituting an acute exposure or "bolus dose") may cause effects substantially different than those associated with long-term low-level exposures. EPA does not currently have a methodology that has Agency-wide approval for dealing with high-level short-term exposures. Consequently, no specific risk values have been provided in this series to evaluate such exposures (although in future revisions such data may be available). A qualitative summary of acute toxicity effects of the target analytes is provided in Section 5. In addition, there are numerous toxicity databases and books that describe the acute toxicity symptoms of the most common contaminants. State agencies may refer to these sources or their local poison control center for guidance on this topic.

Developmental toxicity is often evaluated in animal studies via bolus dose studies, with exposure over 1 to 3 days, because many adverse developmental effects are associated with exposures during critical developmental time periods. Severe

developmental effects including stillbirths have been associated with exposures to high levels of pesticides in foods. Information is provided in a recent NAS report on developmental toxicity on special characteristics of infants and children that cause their exposures and risks to differ from those of adults (NAS, 1993). If very high exposures are likely to occur, State agency staff are encouraged to consider this exposure scenario in more detail.

Risk managers may wish to use other averaging periods (e.g., 7 days, 10 days, or 14 days) for developing short-term consumption limits to better represent vacationers involved in recreational fishing. Using a 10-day averaging period for short-term exposures can be justified for several reasons. Ten days is one of the averaging periods used by the EPA Office of Water in developing Health Advisories for drinking water. It is also relevant to the short time period often considered critical for exposure to developmental toxicants (i.e., there may be a brief window of time during which adverse effects can be induced by toxicants). This time period also corresponds to a typical vacation period. Although some fish consumption advisories use 3 weeks as an exposure period to describe recreational fish consumption (Minnesota Department of Health, 1992; Missouri Department of Health, 1992), no evidence was found to support it as a more accurate period than 10 days. **Note**: Vacationers may identify better with 2-week periods than with 10-day periods (Shubat, 1993a). For this reason, readers intending to develop advisories based on 10-day fish consumption may want to consider expressing consumption limits in terms of a 2-week vacation period instead. As an example, a 10-day meal consumption limit table has been developed for chronic systemic health effects of chlordane is included in Section 3 (Table 3-13). Procedures used to calculate 10-day or other short-term time-averaged consumption limits are described in Section 3.3.6 for those risk managers who want to use these shorter time-averaging periods to better communicate appropriate consumption limits to recreational fishers. **Note**: Those recreational fishers who catch and freeze large quantities of fish to eat later might be considered seasonal or subsistence fishers, depending on the extent of their catch and subsequent consumption.

2.4.3.3 Multiple Species Exposures—

Local information on the consumption of multiple fish species and fish contamination levels can be used to assess exposure and establish consumption limits for consumers with multiple species diets. Equation 2-3 can be modified, as follows, to consider consumption of multiple species:

$$E_{m,j} = \frac{\Sigma (C_{m,j} \cdot CR_j \cdot P_j)}{BW} \qquad (2\text{-}4)$$

where

$E_{m,j}$ = individual exposure to chemical contaminant *m* from ingesting fish species *j* (mg/kg/d)
$C_{m,j}$ = concentration of chemical contaminant *m* in the edible portion of fish species *j* (mg/kg)
CR_j = consumption rate of fish species *j* (kg/d)
P_j = proportion of a given fish species in an individual's diet (unitless)
BW = consumer body weight (kg).

Regional or local angler surveys that estimate catch data and measure fish consumption can provide data on the mix of species eaten by particular populations. One study, the Columbia River Survey (Honstead et al., 1971), is described in Rupp et al. (1979). This survey calculated the total number of each species of river fish eaten by residents in the area. Although the information is a composite of fishers and nonfishers, the data could be used to estimate the mix of species that an average individual in the area would eat. The Columbia River Survey also includes data on the mix of species consumed by each of 10 individuals who ate the most fish during the year, which might be used to estimate exposure for high-risk individuals. Readers may wish to incorporate similar information from local fish consumption surveys into multiple-species exposure assessments and/or consumption limits.

2.4.3.4 Multiple Chemical Exposures—

Fish can be contaminated with more than one chemical, and individuals can consume multiple species of fish that contain different contaminants. In these cases, exposure across species needs to be calculated separately for each chemical; these exposures can then be combined in a variety of ways to estimate risks of different health endpoints. Sections 3.4 and 3.5 provide methods for calculating consumption limits for individuals exposed to multiple contaminants in a single species and multiple species. Readers also may adapt these calculations (Equation 2-4) to estimate individual exposure to multiple fish contaminants.

2.4.4 Population Exposure Assessments

Population exposure assessments are not directly used in developing risk-based consumption limits. Rather, they are primarily used in risk management (e.g., to prioritize resource allocation) and to identify particular subpopulations of interest (e.g., in areas where subsistence fishing is common).

2.4.4.1 Categories of Population Exposure Assessment Information—

Table 2-3 lists the categories of information necessary to evaluate population exposures. Categories 1 and 2 cover basic demographic data that are often available from the U.S. Census Bureau. Categories 3 and 4 relate directly to fish contamination and consumption patterns and should be collected at the local level if possible. Consumption patterns are discussed in greater detail in Appendix D.

Table 2-3. Categories of Information Necessary for a Population Exposure Assessment

1.	Age, sex, and body weight distribution of the population (demographic data)
2.	Average and maximum residence time in an area where exposure is likely to occur
3.	Consumption patterns over the population distribution
4.	Levels of contaminants in fish tissue by species, age (size class), and waterbody
5.	General nutritional status of various segments of the population
6.	Food preparation and cooking methods
7.	Concurrent exposures from other sources to fish contaminants (e.g., occupational, in drinking water or other foods, airborne, soil)

Volume 1 of this series provides guidance on sampling and analysis for fish contaminants as specified in Category 4.

Categories 5, 6 and 7 deal with information, primarily available at the local level, that is important for overall risk assessment. If local information is absent, however, data from populations similar to those of concern may be used. If no local data are available, national data may be used. There are serious limitations to the use of national data, which are discussed in Appendix D. Using data from other populations introduces uncertainties. For example, assuming adequate nutritional status may not be appropriate in an area where nutrition may be impacted adversely by restrictive advisories. Many chemicals pose greater risks to people with poor nutritional status (see Section 5 for a chemical-specific discussion). Consequently, the use of simplifying assumptions may lead to an underestimate of risk (under other circumstances risks may be overestimated). If poor nutrition is suspected in populations with high consumption (e.g., sport or subsistence fishers), obtaining local information is particularly important.

Category 6 deals with information available primarily at the local level on fish preparation and cooking methods. For some chemical contaminants, skinning and trimming the fillet as well as cooking can reduce exposure intake. The effect that fish preparation and various cooking procedures has on reducing contaminant exposure is detailed in Appendix E.

Category 7, which deals with multimedia exposure assessment, may be very significant in some areas. Concurrent exposures are important in estimating overall risk and in determining whether a critical threshold has been reached for threshold effects (i.e., noncarcinogenic effects). Information should be obtained through local sampling programs if possible. If local industries contribute to multimedia and

occupational exposures, the overall assessment may be particularly important. More information on overall exposure assessment and sources of additional information are provided in Section 2.4.5.6.

This information allows the risk assessor to calculate exposure estimates for a population. The information may be collected on various groups within the population (subgroups) who have different consumption rates, culinary patterns, body weights, susceptibilities, etc.

Identification of susceptible subpopulations is necessary to protect these individuals adequately. For pregnant and nursing women, women planning to have children, small children, and people with preexisting health problems, the risk from consuming contaminated fish may be greater than for healthy men and healthy nonreproducing women. Some contaminants are particularly damaging during prenatal or postnatal development. Persons with preexisting health problems may be particularly susceptible to contaminants that interact with their medications or that are toxic to the organ systems affected by disease. For these people, low levels of contaminants may exacerbate their conditions, leading to health effects not generally experienced by healthy adults. (The special susceptibilities associated with the various target analytes are discussed in Section 5.) Due to the above factors, obtaining information on the exposure patterns of susceptible subgroups is important.

In assembling and reviewing this information, keep in mind the goals of the risk management activities for the population being evaluated. Decision-makers should be aware of the information available and the type of information that will enable them to identify those at greatest risk. If resources are limited and only one population subgroup is to be evaluated, evaluating the most highly exposed subgroups rather than the “average” portion of a population may be advisable. The highly exposed groups will provide an estimate of the worst-case scenario. These groups are probably at the greatest health risk (if there is a risk) unless other groups have more susceptible members. Considering the population exposed at an “average” level is also important, but, under most circumstances, they will not be the highest risk group.

Uncertainties and assumptions made in assembling exposure data should be noted and conveyed to the decision-makers. It is important to indicate whether the uncertainties and assumptions are expected to provide overestimates or underestimates of exposure and risk.

2.4.4.2 Categorizing Exposure Levels*—

Exposure assessments for a population describe a distribution of individual exposures. The distribution may be for a geographic area or a particular group of people (e.g., sport fishers at a particular lake, subsistence fishers in a specific Tribe). It is usually advisable to obtain information on the range of average to high exposures. Gathering this information allows the decision-makers to take actions appropriate for the majority of the population and protective of its most at-risk individuals. If sufficient resources to evaluate various aspects of exposure exist, it is recommended that exposure descriptions include the following (Habicht, 1992):

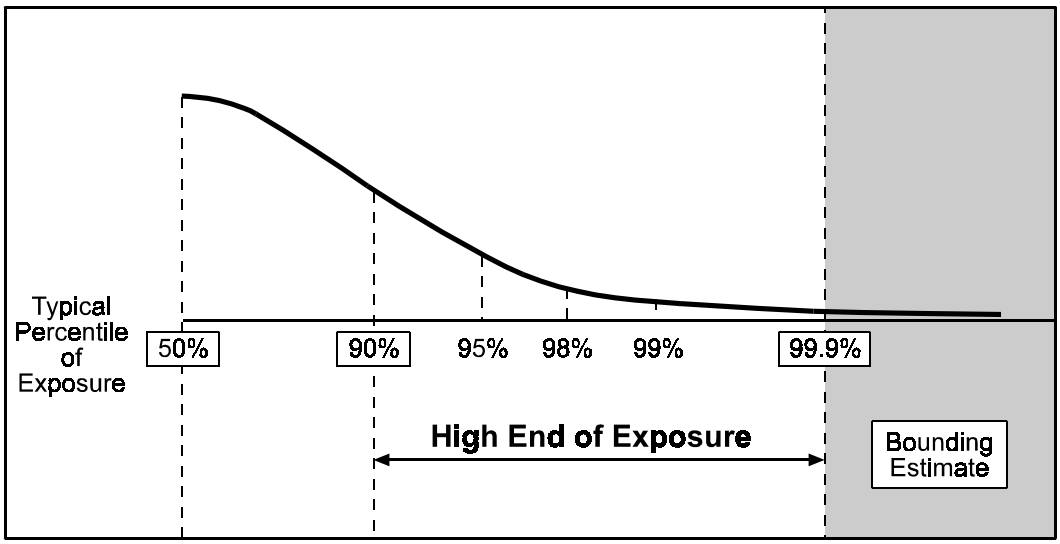
- Individuals at the central tendency and high-end portions of the exposure distribution
- Highly exposed population subgroups
- General population exposure.

This information can be used to estimate the range of risks from the average risk (central tendency) to the most at-risk individuals. The 1992 *Guidelines for Exposure Assessment* provide detailed and specific guidance regarding quantification and description for individuals and populations with higher than average exposure (U.S. EPA, 1992a). This guidance document was the source of information on the various exposure categories discussed below. As with all information provided in this document, these recommendations are provided for reference purposes; State, local, and Tribal governments may elect to use any information they determine is appropriate in establishing fish advisory programs. EPA is currently finalizing a new version of the *Guidelines for Exposure Assessment*. Information regarding the new guidelines will be provided in future editions of this series.

Central Tendency

The central tendency represents the “average” exposure in a population. This value can be derived from either the arithmetic mean or the median exposure level. Figure 2-2 shows the upper half of a normal population exposure distribution. When exposure is distributed normally as in the figure, the mean and median will coincide at the 50th percentile. When the exposure distribution is skewed, however, the mean and median may differ substantially.

* Populations who eat only commercial marine or freshwater fish are not addressed in this guidance because they are protected through regulation of commercial fish by U.S. FDA. Exposure values designed to address consumers of commercially caught fish are not recommended for use in developing fish advisories.



Source: Habicht, 1992.

Figure 2-2. Schematic of Exposure Categories in Upper Half of a Normal Population Distribution.

Due to the skewed nature of many exposure distributions, the arithmetic mean may not be a good indicator of the midpoint of a distribution (e.g., the 50th percentile). Under these circumstances, a median value (e.g., the geometric mean) may provide more appropriate information (Habicht, 1992).

Information on the central tendency of a population's exposure may be most useful in evaluating overall cancer risks and determining the average behavior within a group. It is not as useful in evaluating noncancer risks because such risks are based on a threshold for effects. People exposed at levels above the "average" level may have exposures exceeding the threshold for health effects. If only "average" levels are considered, the risks to these people will not be considered. In a normally distributed population, approximately 50 percent of the population will have exposures above the "average" level.

High-End Portions of the Risk Distribution

The high-end estimates of exposure are those between the 90th and 99.9th percentiles of the actual (either measured or estimated) distribution. They are plausible estimates of individual exposures at the upper end of the exposure distribution. Individuals at the high end of the exposure, dose, and risk distributions may differ, depending on factors such as bioavailability, absorption, intake rates, susceptibility, and other variables (U.S. EPA, 1992a). Risks may be reported at a distribution of high-end percentiles such as the 90th, 95th, and 98th.

Figure 2-2 shows the location of the high-end exposure segment on a normal distribution. High-end exposure estimates include values falling within the actual exposure distribution rather than above it. If all factors (e.g., body weight, intake rates, absorption) are set to values maximizing exposure, an overestimate of exposure will likely result (U.S. EPA, 1992a). High-end exposure estimates are very useful in estimating population risks and establishing exposure limits because they provide a plausible worst-case scenario.

Highly Exposed Subgroups

When a subgroup is expected to have significantly different exposures or doses from that of the larger population, it is useful to evaluate their exposures separately (Habicht, 1992). The subpopulations may differ from the rest of the population by virtue of their activities, age, sex, lifestyle, economic factors, residence, diet, cultural patterns, physiology, or other factors (Habicht, 1992).

Bounding Estimates

A bounding estimate of exposure is greater than the highest actual exposure, corresponding roughly to the upper 99.9th percentile of the population (see Figure 2-2). Bounding estimates are used primarily for screening purposes. Their utility is in providing the decision-maker with a maximum estimate encompassing the entire population (Habicht, 1992). They are most useful in eliminating pathways from further consideration (e.g., if the maximum shows no risk) rather than determining that a pathway is significant (U.S. EPA, 1992a). Although bounding estimates are not recommended for use in estimating risks associated with fish consumption, they may be useful in evaluating the upper bound of risk. Those with no risk at the upper bound can be eliminated from further concern.

Data Gaps

The specific information collected for a population exposure assessment will depend on the goals and resources of the risk managers. Under ideal circumstances, detailed local information would be obtained on each category. When resources are limited, however, assumptions may be necessary for some categories of information. The EPA publication, *Guidelines for Exposure Assessment* (U.S. EPA, 1992a), provides the following options for addressing these data gaps:

- Narrow the scope of the assessment, particularly if the pathway or route with limited data makes a relatively small contribution to the overall exposure.

- Use conservative assumptions. Conservative assumptions, such as choosing a value near the high end of the concentration or intake range, tend to maximize estimates of exposure or dose (U.S. EPA, 1992a). If an upper limit rather than a best estimate is used, express this clearly with the exposure estimate.

- Use models to estimate values and check the conservative nature of assumptions.

- Use surrogate data in cases where a clear relationship can be determined between an agent with usable data and the agent of concern.

- Use professional judgment, especially in cases where experts have years of observation of similar circumstances.

Data gaps can add significantly to the uncertainty associated with exposure and risk assessment. Assumptions may be made or data from nonlocal sources may be used to fill gaps. Selecting health-conservative data will yield health-conservative exposure and risk estimates; alternatively, selecting less conservative data will yield less conservative exposure and risk estimates. Decisions concerning data use will affect risk estimates and may determine where fish advisories are to be provided.

2.4.5 Uncertainty and Assumptions

Readers must evaluate if the exposure assumptions made in deriving risk-based consumption limits provide adequate protection to sensitive or highly exposed populations. Some of the assumptions associated with the exposure parameters can lead to underestimation of total risk (and therefore overestimation of allowable consumption). For example, the calculation of exposure to a given chemical may ignore background sources of that chemical. For chemicals that exhibit health effects based on a threshold level, the combination of background contaminant concentration and fish consumption exposure may exceed the threshold. The use of average fish contaminant concentrations to estimate exposure is another assumption that could underestimate risk if an individual regularly consumes fish from a contaminated waterbody.

Exposure assumptions may not always be sufficiently conservative. However, these assumptions may be balanced by overly conservative assumptions in other aspects of the assessment. Readers need to judge if the overall margin of safety afforded by the use of uncertainty factors and conservative assumptions provides satisfactory protection for fish consumers.

2.4.5.1 Chemical Contaminant Concentrations in Fish—

Exposure quantification requires information concerning fish contamination levels. Volume 1 contains a discussion of sampling and analysis that provides guidance on planning and carrying out a sampling program. The document recommends a two-tiered strategy for monitoring waterbodies for contaminated fish, including:

- Screening waterbodies routinely to identify locations where chemical contaminants in fish exceed levels of concern for human health

- Sampling waterbodies intensely where screening has identified elevated levels to determine the magnitude and geographic extent of the contamination.

Fish contamination varies considerably by waterbody and by fish species and size class. Therefore, even populations with similar consumption patterns may have differing exposures, depending on the contaminant levels in the waterbody used for fishing. To capture these site-specific distinctions, population exposure analyses rely on the use of waterbody-specific data from local surveys on fish contamination. Relevant data from these surveys include levels of contaminants by fish species and size (length and/or weight).

Accurate determination of the chemical concentrations in fish is an important area of uncertainty that is discussed in detail in Section 8 of Volume 1 in this series. The limit of detection (LOD) for each of the 25 target analytes is given in the footnotes of the consumption limit tables in Section 4. The contaminant concentrations in fish tissue below the LOD are shaded where appropriate in Section 4 tables to alert risk assessors to uncertainty in measuring these low concentrations in fish tissue.

2.4.5.2 Dose Modifications Due to Food Preparation and Cooking—

Several sources of uncertainty are associated with the dose modification factors presented in this guidance. Preparation methods are frequently unknown. The effectiveness of different preparation and cooking techniques in reducing contaminant concentrations varies greatly. In addition, information is limited regarding the toxicity of the degradation products generated during the heating of contaminated fish. Percentage reductions observed at one level of contamination may or may not be expected to hold true for different levels of contamination. These sources of uncertainty could lead to either under- or overestimates of exposure. Additional discussion on dose modification may be found in Appendix E.

2.4.5.3 Body Weight—

The estimates for body weight use several assumptions that affect the accuracy of the exposure assessment. First, the figures for body weight are taken from data collected in the late 1970s. Body weights can vary dramatically over time, and therefore the values may be an over- or underestimate of current body weights. In addition, average body weights were not distinguished for various ethnic populations. For example, Southeast Asian-American subsistence fishers may have slighter body frames and lower body weight than the general U.S. adult population. Compared to other assumptions, however, body weight values are associated with relatively low variability and uncertainty. In addition, the consumption limit tables take differences in body weight into account by scaling meal size to body weight (e.g., 8-oz meal per 70-kg body weight).

2.4.5.4 Consumption Rate and Averaging Period—

Fish consumption data are a necessary component of a population exposure assessment. Ideally, fish consumption information will include descriptive

demographic information on the size and location of the fishing population using specific waterbodies; the age and sex of those consuming the fish; the size and frequency of the meals (over the short and long term); and the species of fish caught, portions of the fish consumed, and methods of fish preparation and cooking. This section discusses the selection of fish consumption data and presents results obtained in numerous studies.

In general, fish consumption studies describe:

- Species of fish consumed by various subgroups within a population
- Temporal patterns of consumption
- Variety of preparation and cooking methods used by different populations.

Many studies provide some, but not all, of the above data.

Consumption patterns may differ significantly both within and between populations. Studies of fish consumption indicate that some groups within the general U.S. population may consume considerably greater quantities of fish than other members of the population.

This document focuses on noncommercial fishers (i.e., people who fish and consume their catch) and the people with whom they share their catch. This subpopulation may include sport fishers and subsistence fishers. Sport fishers include all noncommercial fishers who are not subsistence fishers. (They have also been referred to as recreational fishers.) Subsistence fishers, as previously defined, include people who rely on noncommercial fish as a major source of protein. Subsistence fishers may also catch fish for commercial sale; however, this activity comes under the jurisdiction of the FDA and is not considered in this document. There is often not a clear distinction between sport and subsistence fishers. Many individuals would not consider themselves subsistence fishers but do rely on noncommercially caught fish for a substantial portion of their diet. The mean or median estimates of consumption rates and patterns generally address the more casual sport fisher; the high-end estimates (upper percentiles) and patterns address the consumers at greater risk. In many of the older surveys, the high-end estimates were used as estimates of the consumption rates for all subsistence fishers. These estimates, however, may be inaccurate because some surveys excluded subpopulations that tended not to register for fishing licenses.

The two most sensitive variables involved in calculating individual exposure often are consumption rate and averaging period. Consumers of noncommercially caught fish differ immensely in their consumption habits. Some may consume fish for 1 week during a year or for several weekends each year (e.g., as recreational or sport fishers). Others may consume fish for much longer periods during a year (seasonal fishers) or may rely on fish year-round as a major part of their diet (subsistence fishers). Within these groups, some individuals are more susceptible to contaminants, including women of reproductive age, children, and persons with preexisting health problems.

Short-term recreational and seasonal fishers are assumed to be exposed to contaminated fish for only part of the year. Recreational vacation fishers are those who eat fish only a short time during the year. Seasonal fishers are often those who live near a lake or river, who fish regularly throughout a season (e.g., summer fishing, winter ice fishing), and who eat their catch throughout the season but do not rely on fish as a major dietary staple during the rest of the year. Sport fishers have been shown to have higher fish consumption rates than the general U.S. population (U.S. EPA, 1989a); the potential for large exposures over short time periods makes them especially susceptible to acute, developmental, and subchronic health risks as compared to nonfishers.

Subsistence fishers eat fish as a major staple in their diets for a greater percentage of the year than do recreational fishers. In addition, subsistence fishers may prepare fish differently than do other groups; they may use the whole fish in soups or consume more highly contaminated tissues, such as the liver, brains, and subcutaneous fat. Both their longer exposure durations and consumption habits make many subsistence fishers more likely to be affected by cancer and adverse chronic systemic, developmental, and reproductive health effects resulting from fish contaminant exposure than those who do not fish or fish for shorter periods of time. Some populations who may subsist on noncommercially caught fish year-round, including Native Americans and certain recent immigrants accustomed to self-sufficiency and fishing (particularly Asian-Americans) and economically disadvantaged populations may be particularly at risk since much of their fishing might be expected to occur in more urbanized areas with higher levels of water pollution.

Any estimates of typical fish consumption patterns in a population include certain assumptions. West et al. (1989) described variations in fish consumption in communities in Michigan by ethnicity, income, and length of residence. In general, African Americans and Native Americans ate more fish than Caucasians; older individuals ate more fish than younger individuals; individuals with lower incomes tended to consume greater quantities of fish than individuals with higher incomes; and longer-term residents of the communities tended to consume more fish than other individuals. To the extent that members of the target population have characteristics associated with higher-than-average consumption, the recommended consumption values may underestimate their consumption. Unless surveyed specifically, subsistence fishers may be underrepresented by available surveys. Surveys associated with the issuance of fishing licenses are traditional mechanisms used in surveying fish consumption behavior; however, subsistence fishers may not apply for fishing permits or licenses. For example, Native Americans on reservations do not need fishing permits, and often times other groups (e.g., recent immigrants or the elderly) may not know that they need to have a license or find them too expensive to buy.

In addition, fish consumption limits that are based on single species for single chemicals do not account for exposures from multiple chemicals contaminating a single species or for multiple species diets. Consumption limits that focus on a single waterbody do not account for the possibility that consumption can occur

from a variety of waterbodies. Single-species consumption limits also do not address related species that may be contaminated but were not sampled. Such consumption limits could seriously underprotect persons who eat a variety of fish species from a number of waterbodies. Readers need to decide if consumption limits have a wide enough margin of safety to protect such consumers.

Other methodological assumptions may also lead to increased uncertainty. The calculation of consumption limits that express allowable dose as a number of meals over a given time period may neglect potential acute effects if consumption occurs over a very short time period. For example, a meal limit of two meals per month conceivably could be interpreted by consumers to mean that two meals on 1 day in a given month is allowable; this behavior could lead to short-term acute effects. This could be avoided by always expressing the consumption in terms of the time interval in which one meal may be consumed, (e.g., one meal per 2 weeks, rather than two meals per month).

The use of averaging periods treats large, short-term doses as toxicologically equivalent to smaller, long-term exposures when comparing exposure to the toxicity reference value. This assumption may underestimate the potential toxicity to humans if the toxicity depends on a mechanism sensitive to large, intermittent doses. (This may occur more often with acute and developmental effects than with other effects.)

The averaging period of 1 month used in this document is based primarily on the types of health data currently available and the risk assessment methods recommended by EPA. Consequently, there is no acute exposure methodology recommended (that would correspond to bolus doses; see Section 2.3) in this document. In subsequent editions, this type of information may be included.

2.4.5.5 Multiple Species and Multiple Contaminants—

As discussed above, individuals often eat more than one species of noncommercially caught fish in their diet. If consumption limits or exposure assessments consider only a single-species diet, exposure from contaminated fish could be underestimated if other species have higher concentrations than the species under consideration. On the other hand, an exposure assessment may be overprotective if an individual's diet is a mix between contaminated and uncontaminated species. Use of local information to the extent possible to characterize mixed diets can prevent some of this uncertainty.

An individual may consume a given species that is contaminated with multiple chemicals, or may consume several species, each with different contaminants, or both. In these circumstances, exposure assessments that examine contaminants individually in individual species will underestimate exposure. This situation may be avoided by using Equation 2-4 in Section 2.4.3.3 for multiple species exposures and characterizing exposure to all known contaminants for a given individual. These exposure values can be used in methods described in Sections 3.4 and 3.5 to set consumption limits based on multiple species and multiple contaminants.

2.4.5.6 Other Sources of Exposure—

The methods described in this guidance consider exposure primarily from consumption of noncommercially caught fish. This approach may lead to an underestimation of exposure and, consequently, an underestimation of risk for some contaminants. Additional background exposure may cause individuals exposed to fish contaminants through other contaminant sources (e.g., other foods, drinking water, inhalation, or dermal contact) to experience negative health effects and/or increased cancer incidence, even if they abide by the consumption rates recommended in fish consumption advisories. State agencies are encouraged to use available information on other sources of exposure whenever possible in setting consumption limits or to set the limits so that the allowable consumption accounts for only a fraction of the total allowable daily dose. These approaches would allow a margin of safety to guard against the potential for background exposure leading to an exceedence of contaminant thresholds and/or maximum acceptable risk levels.

Nonfish Sources of Exposure

People may be exposed to one or more of the target analytes through sources or pathways other than noncommercially caught fish. These pathways include contaminants found in or on commercially caught fish, other food, drinking water, air, or other materials (e.g., soil or sediment).

Contact may often occur via more than one route of exposure (e.g., ingestion and dermal contact with contaminants in soil). The possibility of exposure via other pathways dictates that caution be used in setting health safety standards that do not take these other sources into account. The total exposures may cause the individual to exceed a safe exposure level, even though the exposure via fish consumption alone may be safe.

EPA is currently developing a relative source contribution method, which can be used to evaluate the amount of exposure contributed from various sources. The RSC method can be used to compare total contaminant exposure to that contributed by a specific source (e.g., fish); it is also useful in evaluating the total exposure from all sources. Information on the relative contribution of fish to overall exposure can be used to develop advisories that recommend sufficiently low exposure to ensure that total daily exposure is below an established targeted exposure level (e.g., an RfD). It is anticipated that information regarding the RSC method will be incorporated into future revisions of this document.

If State agencies have information about other pathways that may contribute significantly to exposure, then risk assessors are encouraged to use this information to calculate an appropriate total exposure limit. An alternative approach may be appropriate when nonfish exposures are suspected but have not been quantified. Depending on the magnitude of the suspected nonfish exposure, the fish advisory intake limits may be set at a level that accounts for some fraction of the total allowable daily dose (e.g., 10, 20, or 30 percent). This allocates to the

nonfish exposures the remaining percentage of the total exposure limit. The goal of both of these strategies is to ensure that the total pollutant exposure does not exceed the predetermined exposure limit.

One State program raised concerns that this series focuses on reductions in exposure via fish when exposures via multiple media may be occurring. However, it is important to note that, although exposure reductions can theoretically be made in any contaminated media, fish consumption may be the only source that can be readily reduced. It may not be possible to reduce air, drinking water, or other contaminant levels quickly, yet fish advisories have the potential for rapid exposure reduction in a population. Because fish consumption may contribute significantly to overall exposure for some population groups, modified consumption patterns may reduce overall exposure considerably. The relationship between fish and other contaminant source contributions to overall exposure should be communicated to risk managers so that both short- and long-range planning for exposure reduction can occur.

Estimating Total Exposure

The following discussion of exposure calculations is similar to that provided in Section 2.4.3 for individual exposure assessment. Exposure assessments provide descriptions of the overall, contaminant-specific, media-specific, or population-specific exposure of an individual or similarly exposed group. The following equation may be used to express exposure in a manner (mg/kg/d) that can be easily compared to an RfD or used to calculate cancer risks:

$$E_T = \frac{C_m \cdot CR}{BW} + E_A + E_W + E_F + E_O \qquad (2\text{-}5)$$

where

E_T = exposure from all sources (mg/kg/d) to contaminant (m)
C_m = concentration in the edible portion of fish (mg/g)
CR = mean daily consumption rate of fish (g/d)
BW = average body weight of the group (kg)
E_A = exposure from air sources (mg/kg/d)
E_W = exposure from water sources (mg/kg/d)
E_F = exposure from nonfish food sources (mg/kg/d)
E_O = exposure from other sources (e.g., soil)(mg/kg/d).

The equation expressing average daily consumption per kilogram in Appendix D can also be used to express fish-borne exposure (the C_m, CR, and BW portion of the equation). If the concentration in fish tissues is reduced due to preparation or cooking, the C_m value should be modified accordingly. Note that loss of contaminants, with a proportional loss of fillet weight, will not change the concentration, which is expressed in milligrams of contaminant per kilogram of fish

(mg/kg). Finally, the daily exposure (mg/d) is divided by consumer body weight (BW) to arrive at individual daily intake (mg/kg/d).

Body weights for various age groups of consumers are summarized in Table 3-8. If high estimates of body weight are used (e.g., adult male values), the risks and fish advisories will be less health conservative. If lower body weights are used (e.g., for small women), the risks and fish advisories will be more health conservative. When children's exposure is evaluated separately, their body weights should be used in conjunction with their estimated consumption rates. Risk managers may wish to consider whom they are designing the fish advisories to protect, and whether they wish to protect the most at-risk groups in selecting a body weight. The selection of a body weight value will not have a substantial impact on the final values because the differences in body weight are relatively small (less than a factor of 2) compared to the uncertainties associated with most toxicological data.

Methods for estimating exposure to multiple contaminants and multiple fish species are discussed in Section 3 and equations are provided. These equations for individual exposure estimates can also be used for populations with similar exposure characteristics.

The type of exposure information collected and evaluated will depend on the resources and goals of the fish advisory program. Under ideal circumstances, pollutant levels would be evaluated in all media to which individuals may be exposed. For example, drinking water contaminant levels may be evaluated by the local water purveyor on a regular basis, and this information can be used to estimate waterborne exposure. When pesticides are the subject of concern, the evaluation may be more difficult because the levels present in food are not evaluated frequently at the local level. In addition to providing necessary information for the development of fish advisories, a total exposure assessment may highlight nonfish sources of exposure that merit attention.

Summarizing Exposure Information

Table 2-4 is a template for use in summarizing exposure information. It contains entry areas for fish exposure and exposure via other media. Risk assessors and managers may wish to use this template to organize their exposure data for various population groups or subgroups by chemical. The table is designed to organize data obtained from a specific location (e.g., an area adjacent to part of a waterbody or surrounding an entire waterbody). It is anticipated that the information entered in this table would be organized according to population subgroups with similar risk characteristics (i.e., a separate table should be prepared for children, women, etc).

As noted earlier, exposure levels may differ among subgroups within the fish-consuming population, depending on the species of fish that are caught, the quantity of fish consumed, and the method of preparation and cooking used. In some cases, other factors will also affect exposure (e.g., seasonal changes in contaminant levels, the age of the fish). For purposes of risk assessment,

Table 2-4. Exposure Data Template

Location:

Population Subgroup (e.g., children, women 18-45 yr, etc.):

Population Size:

Body Weight:

Contaminant (level)	Fish Exposure Estimates (mg/kg/d)		Other Exposures								Subtotal of Other Exposures (mg/kg/d)		Total of All Exposures (mg/kg/d)	
			Air (mg/kg/d)		Water (mg/kg/d)		Food (mg/kg/d)		Other (e.g., soil) (mg/kg/d)					
	Central	High End[a]	Central	High End	Central	High End	Central	High End	Central	High End	Central	High End	Central	High End

[a]Risk assessors may wish to use a bounding estimate rather than a high end estimate (or both).

specifically targeted risk information is obtained when the exposure of a population group is the same and their susceptibilities to the chemicals of interest are the same.

Estimates may be made for average, high-end, or upper-bound exposures within a population group. The use of average exposure values is not recommended because approximately one-half of the population will have exposures greater than the average (by definition). High-end estimates maximize the protection of public health. Upper-bound values may yield unrealistically high estimates of exposure and risk and are more appropriate for screening purposes than for risk assessment. Depending on the characteristics and needs of the fisher population, risk managers may elect to use the values they deem most appropriate.

The template provides entry areas for central tendency, high-end exposure, and bounding estimates. By including these categories of information, risk assessors can calculate a wider range of risk estimates and risk managers will have more complete information on which to base decisions regarding appropriate fish advisories. It may not be practical, however, to do three levels of calculations for each area, group, and contaminant. Table 2-4 does not contain a separate entry column for dose modifications due to cooking or cleaning. If these activities are known to reduce exposure, risk assessors may enter appropriately reduced exposure values to account for the dose reduction (see Appendix E for additional information).

The information entered in Table 2-4 will be used with risk values to calculate risks. For this reason, body weight, an essential component of risk calculations, is included. It is assumed that body weights corresponding to the population of interest will be used. For example, if specific calculations are to be carried out for women exposed to mercury, then a separate exposure table (or entry) for women, using appropriate consumption and body weight values, is advisable. Similarly, if risks are to be estimated for children or separate advisories are to be developed for this group, information regarding children's exposure would be entered separately.

Exposures to contaminants from media other than fish may vary considerably for children in comparison to adults. Children have higher intakes of food, drinking water, soil, and air in relation to their body weight than do adults (NAS, 1993). In particular, infants consume significantly greater amounts of fluid than older children and adults. If contaminants are known or thought to occur in water supplies, infants may be a subpopulation for whom a separate analysis would be warranted, especially if water is used to mix formula. If the contaminant of concern is concentrated in human breast milk, breast-fed infants may be at greater risk.

Any exposure information that will modify the total exposure of the target population may be entered in the template to indicate their differences from the larger population. Situations such as workplace exposure, high periodic fish consumption, or other occurrences can be noted and evaluated for their impact on overall health and risk.

2.5 RISK CHARACTERIZATION

In general, the risk characterization step of the risk assessment process combines the information for hazard identification, dose-response assessment and exposure assessment in a comprehensive way that allows the evaluation of the nature and extent of risk (Barnes and Dourson, 1988). Risk characterization can be used by risk managers to prioritize resource allocation and identify specific at-risk populations; it is also used to establish regulations or guidelines and to estimate individual or population risk. In this document, risk characterization has been used to develop the risk-based consumption limits provided in Section 4. The methods involved in developing consumption limits are described in detail in Section 3 and are not repeated here. When risk characterization is used to estimate individual or population risk, it serves to provide the risk manager with necessary information regarding the probable nature and distribution of health risks associated with various contaminants and contaminant levels.

Risk characterization in general has two components: presentation of numerical risk estimates, and presentation of the framework in which risk managers can judge estimates of risk (U.S. EPA, 1986a). A characterization of risk, therefore, needs to include not only numerical characterizations of risk, but also a discussion of strengths and weaknesses of hazard identification, dose-response assessment, and exposure and risk estimates; major assumptions and judgments should be made explicit and uncertainties elucidated (U.S. EPA, 1986a).

Numerical presentations of risk can include either estimates of individual risk or risks across a population. For example, for cancer risks, numerical estimates can be expressed as the additional lifetime risk of cancer for an individual or the additional number of cases that could occur over the exposed population during a given time period. Numerical risk estimates can also be expressed as the dose corresponding to a given level of concern (U.S. EPA, 1986a). These values can be used to estimate the environmental concentration or contact rate below which unacceptable health risks are not expected to occur. For the determination of fish advisories, the environmental concentration takes the form of screening values (i.e., contaminant concentrations in fish, as discussed in Volume 1) and the contact rate takes the form of risk-based consumption limits for specified populations.

Additional factors to be considered in risk characterization include:

- Possible exposure to the fish contaminant(s) from additional sources (e.g., air, water, soil, food other than fish, occupational activities)

- Characteristics of the population that may cause them to be more susceptible than the general population due to exposures to other toxicants, their general health and nutritional status, or their age

- An absence of sensitive study data for significant health endpoints such as developmental abnormalities, neurotoxicity, and immunotoxicity

- Recent toxicological study results indicating potential health risks not considered in the current risk values

- Information from local medical practitioners indicating likely risk-related health effects

- Economic, nutrition, or other hardships that may result from fishing restrictions.

Most of the factors listed above may lead a State agency to select more health-conservative risk values. For example, when information regarding a population (or subgroup) indicates that they have poor nutritional status that may increase their susceptibility to a local contaminant, State agencies may elect to modify the risk values they are using directly to provide an additional "margin of safety." Although the RfDs are designed to protect the most sensitive individuals, State agencies have discretion in determining the appropriate approach to protecting the public health of the people they serve.

The last factor listed above is an important risk management consideration. Use of health-conservative risk values will result in more restrictive fish advisories, which may have serious impacts on local populations.

In many cases the advantages and disadvantages of selecting specific risk values will affect members of communities in different ways. Groups at highest risk will be the most likely to gain from being alerted to health hazards (if they choose to take protective action). Alternatively, groups with relatively low risks may unnecessarily avoid consumption of food or participation in the sport of fishing, even though these may have overall benefits to them (i.e., the risks may be outweighed by the benefits).

There will invariably be tradeoffs between protection of public health and unwanted impacts of consumption restrictions. In some cases, the benefits of advisories may be a generally agreed-upon community value (e.g., preventing relatively high risks to pregnant women). Other cases may be less clear, especially when the scientific evidence on risks is limited. Decision-makers are urged to consider the scientific information, fish consumption patterns, community characteristics, and other local factors carefully, along with potential positive and negative impacts of their decisions, when selecting risk values for screening or establishing advisory limits. Involving the affected communities in the decision-making process may be advisable under most circumstances.

See Appendix F for EPA's guidance for risk characterization, which discusses the basic principles of risk characterization.

2.5.1 Carcinogenic Toxicity

In this guidance series, screening values are defined as the concentrations of target analytes in fish tissue that are of potential public health concern and that are used as standards against which levels of contamination can be compared. For

carcinogens, EPA recommends basing screening values on chemical-specific cancer slope factors. Screening values are used to establish the concentration in fish that can trigger further investigation and/or consideration of fish advisories for the waterbodies and species where such concentrations occur. The method for calculating screening values is given in Volume 1 of this series.

2.5.1.1 Individual Risk—

Using cancer slope factor and exposure data in mg/kg/d, cancer risks are calculated using the equation:

$$\text{Lifetime risk} = \text{exposure} \times \text{cancer potency}$$

where

exposure = total exposure to a single contaminant from all sources (mg/kg/d)
cancer potency = upper bound of the lifetime cancer risk per mg/kg/d.

Note that cancer risk can be estimated for individual sources of exposure. Use of the total exposure value yields an estimate of lifetime cancer risk from all sources of a single contaminant. The resulting value is the upper bound of the estimated lifetime cancer risk for an individual or for a group with the same exposure level. Different exposure levels may be used in the above equation to calculate risks for different groups within a population having differing consumption rates, body weights, etc.

EPA cancer slope factors are based on an assumed exposure over a lifetime; consequently, adjustment for differences in consumption and body weight in childhood may not be necessary. Based on the occurrence of some childhood cancers, it is suspected that exposure to some chemicals may not require a lifetime to generate risk. However, carcinogenic toxicity tests in animals are usually conducted for the lifetime of the animal. Consequently, it is not possible to determine, for most contaminants, if there are risks that may be generated with a brief exposure duration. This remains an area of uncertainty. When human data are available, which is relatively rare, impacts on children are often better understood (e.g., risks are well known for ionizing γ radiation). State agencies should evaluate their approach to this issue based on their review of the available literature.

2.5.1.2 Population Risk—

The estimated population cancer risk is calculated by multiplying the number of people in an exposure group (with the same exposure) by the lifetime cancer risks calculated from the equation above. The population risk equation is:

$$\text{(population cancer risk)} = \text{lifetime risk} \times \text{(size of exposed population)}.$$

For example, if 5,000 people are exposed at a risk level of one per thousand (1×10^{3}) (per lifetime), the overall risk to that population is five additional cancer cases ($5{,}000 \times 1 \times 10^{-3} = 5$) over the background level.

When different exposure levels occur, this calculation is repeated for each exposure group. The total risk is the sum of the risks at each exposure level:

total risk = risk at exposure level a + risk at exposure level b + . . . risk at exposure level n

Likewise, when multiple contaminant exposures occur, the total risk will equal the sum of the risks from individual contaminants at each exposure level.

2.5.2 Noncarcinogenic Toxicity

For chronic systemic toxicants, the RfD is used as a reference point in assessing risk. The RfD is calculated so that there is little probability of an adverse health effect occurring due to chronic exposure to chemical concentrations below the RfD. Exceedence of the RfD implies there may be some risk of the adverse health effect occurring; however, the magnitude of risk and severity of the effect are not quantified by this approach.

2.5.2.1 Individual Risk—

The comparison of exposure to the RfD indicates the degree to which exposure is greater or less than the RfD. The following equation expresses this relationship:

$$\text{ratio} = \text{exposure}/\text{RfD}$$

where

exposure = total exposure to a single contaminant from all sources (mg/kg/d)
RfD = reference dose or other noncarcinogenic exposure limit.

When the ratio obtained in the above equation is equal to or greater than 1 (i.e., when exposure exceeds the RfD), the exposed populations may be at risk. Although a margin of safety is incorporated into RfDs (see Section 2.3), actual thresholds are usually not known. Consequently, exposure above the RfD is not recommended. The likelihood of risk is related to the degree to which exposure exceeds the RfD. Risk also depends on individual characteristics; susceptibility to toxic exposures varies considerably in most populations. Consequently, the primary use of RfDs is to provide a protective exposure limit rather than to predict risks. In practice, however, they are often used to estimate risk.

2.5.2.2 Population Risk—

The population risk is expressed as the number of individuals with exposure levels greater than the RfD:

noncarcinogenic risk = population with exposure greater than the RfD.

Reviewing the health basis for the risk estimate is useful when evaluating the risk estimates. A wide range of effects is used to establish RfDs. Some are very serious (e.g., retarded growth, liver damage, infertility, brain dysfunction) and others are of less concern (e.g., changes in enzyme levels indicative of preliminary stages of toxicity). In most cases the less serious effects will lead to serious effects as exposure levels increase above the RfD. This type of toxicity information should be considered when reviewing risk estimates.

Nonfish sources of exposure may be an important contributor to overall exposure. In some cases, exposure to a contaminant via fish consumption alone may not generate risk at the population's consumption level, but exposure to the contaminant in fish and other foods, water, soil, or air may exceed the RfD. Total exposure information can be used to obtain a much more accurate assessment of risk. When exposure occurs via other sources, the lack of total exposure assessment leads to an underestimate of exposure, and potentially of risk. Accurate risk information provides a more appropriate basis for decisions regarding the need for fish advisories.

An alternative approach is to express the dose as the magnitude by which the NOAEL exceeds the estimated dose (termed the margin of exposure, or the MOE). Where the MOE is greater than the product of the uncertainty and modifying factors (used in calculating an RfD from a NOAEL), then concern is considered to be low (Barnes and Dourson, 1988).

2.5.3 Subpopulation Considerations

A major goal in evaluating population risks is the identification of target populations. This document defines target populations as fish consumers determined by decision-makers to be in need of fish advisory programs. This section discusses the criteria for such a decision.

The identification of target populations involves both risk assessors and risk managers and requires both scientific and policy judgments.

A population would usually be targeted because they consume fish with contaminants that may pose health hazards. In some cases, they may have known high exposures; in other cases, State agencies may have limited information suggesting they are at risk. Regardless of the supporting data available, determining who the target populations are is a critical step in establishing a fish advisory program.

A risk-based approach can be used to identify target populations. This approach requires decisions concerning the level of "acceptable" risk for carcinogenic and noncarcinogenic effects. For example, a health agency may determine that any population with cancer risk levels greater than 1 in 1 million requires a consumption advisory. For noncarcinogenic effects, exposures greater than the

RfD by a factor of 1, 10, or some other values may be chosen to determine which groups require protection under a fish advisory program. Establishing an exposure limit for the purposes of identifying at-risk populations enables State agencies to equitably screen populations to determine where action is needed. Different subgroups within a population will often have differing consumption rates and may need to be considered individually to adequately address their levels of risk and need for program assistance. For example, children consuming contaminated fish at a rate that is safe for adults may be at risk due to their small body size and increased intake, per unit of body weight (mg/kg/d). Choosing the levels at which populations are determined to need such advisories is a policy decision.

Defining acceptable risk has been a difficult problem at both the Federal and local level. Federal programs have targeted various levels of cancer risk in developing regulations and guidance, and these levels often change over time and may be modified based on the needs of particular areas. “Acceptable” risk has also been defined and redefined in a number of legal cases.

Decisions regarding acceptable risk levels are often considered high-level policy decisions because they may affect the public’s health directly. Many States have specific guidance written into their legislation regarding benchmark levels of risk (e.g., 1 in 1 million cancer risk is targeted in New Jersey for drinking water contaminants, modified by feasibility considerations).

Due to the important nature of decisions concerning acceptable risk levels, State agencies are encouraged to seek input from a variety of sources, including target populations, when establishing these levels. The selection of specific groups as target populations is a critical decision because it affects who will be served, the levels of potential risk of those who will not be served, and the scope of the fish advisory program needed. EPA encourages States, local, and Tribal governments to consider the most sensitive populations when establishing programs. “Sensitive” in this context means those people who are at greatest risk due to their exposure, age, predisposing conditions, or other factors.

Some population groups may warrant more restrictive risk levels (e.g., children may be considered more susceptible than some other subgroups); however, levels of protection and provisions of services should be equitable across all people served.

Some contaminants have very well-supported risk values. Others have values that are based on limited data, or the data suggest risks may occur that are not quantitatively definable at this time. In these cases, State agencies may choose to consider risks from a more health conservative viewpoint. Alternatively, the risk values could be modified by State agencies to calculate risks reflecting these concerns. The use of risk data, and its impact on populations and how fish advisory programs are designed, is at the discretion of State, local, and Tribal agencies. Some chemicals have information available, but the data are not sufficient to quantify the risk to sensitive subpopulations. For example, DDT is

thought to cause effects in two sensitive populations for which no quantitative dose-response data exist. Based on animal studies, DDT may cause cardiac sensitization leading to ventricular fibrillation and death (Hayes, 1982). However, there are insufficient data to relate this quantitatively to human populations that have cardiac disorders or other stresses that could make them especially susceptible to these effects. DDT may also cause disturbances in the normal reproductive system of females (Hayes, 1982), although, again, no quantitative dose-response data exist for these effects. Another example is that certain chemicals (such as organophosphate pesticides) are metabolized more slowly in certain individuals with specific enzyme deficiencies than in the general population (Hayes, 1982). The dose-response data for these effects are not available. In all these cases, the probability or the magnitude of the response that may result from a given dose cannot be quantified adequately. Information on these effects of DDT on sensitive subpopulations and other chemicals that may result in risk to certain sensitive populations are described in Section 5. Readers can use this information in several ways. Sections 2.3.2.2 and 2.3.2.3 briefly discuss methods for applying modifying factors to the toxicity reference values in cases where there are insufficient data to quantify risks. Readers may also choose to consider these effects qualitatively when developing consumption limits and/or making risk assessments. In addition, consumption advisories can contain a discussion of suspected effects of a given chemical for particular subpopulations, so that individuals with such conditions can make informed decisions regarding their consumption of fish. Finally, readers may wish to apply an additional safety factor to the meal advice aimed at such populations to provide some measure of additional protection.

2.5.4 Multiple Species and Multiple Contaminant Considerations

Readers are encouraged to take multiple species consumption and/or multiple contaminant exposures into account when developing consumption limits and/or assessing risk. Methods for doing so are described in Sections 2.4.5.4, 3.4, and 3.5.

2.5.5 Incorporating Considerations of Uncertainty in Consumption Limits

Previous sections have discussed the many uncertainties associated with the estimates of exposure and toxicity data assessments that form the basis of the risk assessment and the derivation of risk-based consumption limits. Readers may wish to estimate the direction the uncertainties are likely to have on the risk estimates (i.e., do these uncertainties tend to exaggerate or diminish potential risk). The assumptions made in the risk assessments to account for uncertainties need to be clearly outlined (e.g., Section 2.3.5 contains a description of the nature of the uncertainties associated with each uncertainty factor applied in deriving an RfD). The use of the 95 percent upper confidence limit for the slope of the dose-response function at low doses for carcinogens is an example of a conservative assumption imbedded in most cancer slope factors. Likewise, exposure assessments frequently include conservative assumptions where data on actual exposure are absent, such as the assumption that no dose modification occurs when the

cooking and preparation methods of target populations are unknown. Where possible, readers are encouraged to attempt to quantify the magnitude of the effect of such assumptions on the numerical risk estimates.

2.6 SUMMARIZING RISK DATA

This section provides methods to summarize population exposure and risk. The risk assessment process can generate considerable data on various populations and geographic areas with details on numerous contaminants and levels of exposure. Organization of these data is useful so that the results can be reviewed in a meaningful way. Because different circumstances will require different data arrays, a number of templates are provided (Tables 2-5, 2-6, and 2-7) for organizing risk information for various purposes.

The presentation of the templates proceeds from the most specific (risk levels for a specific population at a specific waterbody) to more general risk summaries for a large geographic area. The templates are offered as a convenience and may contain entry areas that are not appropriate for all circumstances. State agency staff are encouraged to modify these or omit areas as needed.

Table 2-5 is a template that can be used to organize exposure data, risk values, and risk estimates. It is designed to be used for a specific population in a specific location with exposure to a contaminant at a known level. This table provides entry areas for the various factors that are used in calculating risk, as well as the actual risk estimates. Depending on the type of contaminants present and population characteristics, estimating risks for various subgroups may be advisable. This data display will allow agencies to highlight which groups within a population are at highest risk and to summarize the risks to a particular population. This table can also be used to evaluate the varied impacts on risk that may occur as a result of changing assumptions regarding consumption patterns, contaminant concentrations, and risk values.

Fish contaminants and contaminant concentrations are listed in the left column. If different concentrations are expected in different size fish, different tables can be developed for the various concentrations. Table 2-5 includes entries for central tendencies, high-end, and bounding exposure and risk estimates. It is not expected that all these variables will be calculated for all groups and conditions. This information, however, provides a range of estimates that can be used in prioritizing activities and designing appropriate programs. The template has entry areas for both fish and nonfish exposures.

Some agencies may not have information on nonfish exposures or may choose not to evaluate other sources of exposure in determining appropriate fish advisories. Risk assessors may modify the categories of information listed in this table to suit the specific characteristics of their local populations and fish advisory programs.

Table 2-5. Risk Estimates

Location:
Population:
Population Size:
Contaminant:
Contaminant Concentration:

Specific Subgroups	Fish Exposure Estimates		Other Exposures	Subtotal of Other Exposures		Total All Exposures		Risk Values			Other Factors (e.g., special susceptibilities due to nutritional status, disease, etc.)
	Central Tendency	High-End Estimate[a]		Central Tendency	High-End Estimate	Central Tendency	High-End Estimate	Non-carcinogen	Carcinogen	Alternatives	
Total Population											
<18 yr											
>18 yr											
Women, 18-45											

Risk Estimate

Central Tendency						High-End Estimate					
Noncarcinogen (% of RfD)		Carcinogen (Lifetime Risk)		Alternatives (% of Alternatives)		Noncarcinogen (% of RfD)		Carcinogen (Lifetime Risk)		Alternatives (% of Alternatives)	
Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures

[a]Bounding estimate may also be used.

Table 2-6. Risk Characterization

Location:

Population:

Population Size:

Contaminant Level (mg/kg)	Total					
	Central Tendency			High-End Estimate or Bounding Estimate		
	Carcinogen (Lifetime Risk)	Noncarcinogen (% of RfD)	Alternatives (% of Altern.)	Carcinogen (Lifetime Risk)	Noncarcinogen (% of RfD)	Alternatives (% of Altern.)

Table 2-7. Risk Summaries for a Waterbody

Population Group	Risk Estimates Based on High-End Exposures		
	Cancer Risks	Noncancer Risks	Other Risks
Total Population A			
<18 yr			
>18 yr			
Women 18-45 yr			
Total Population B			
<18 yr			
>18 yr			
Women 18-45 yr			
Total Population C			
<18 yr			
>18 yr			
Women 18-45 yr			
Aggregate of A,B,C			
<18 yr			
>18 yr			
Women 18-45 yr			

Table 2-5 also provides information lines for risks to women 18 to 45 years of age, the reproductive age for many women. This separate entry area was provided because many health officials are particularly concerned about developmental effects that may arise from exposure to long-term or bolus doses of fish contaminants, especially mercury. Separate entry areas for children were also provided because their consumption in relation to their body weight is often greater than that of adults. Consequently, their risks may be higher for noncarcinogens (carcinogenic risk estimates are based on a lifetime exposure, including childhood).

Evaluation of the risks to multiple groups may be warranted when more than one population uses a particular waterbody. Under those circumstances, various data summaries may be needed to provide data for differing fish advisories. For

example, sport fishers and subsistence fishers may use the same waterbody but have different risks based on their varied consumption habits.

Table 2-5 provides entry areas for the various factors used to calculate risk. State agencies may wish to use this format to evaluate the sensitivity of the final risk estimates to variations in input factors such as fish exposure, other exposures, risk values, contaminant concentrations, and body weight. This type of sensitivity analysis will provide information on the importance of the various factors. When uncertainty exists about one of the inputs, such as a risk value or contaminant level, its relative importance in the overall estimates of risk can be evaluated.

Table 2-6 provides a template to be used to summarize risk data for a specific population, using information presented in Table 2-5. This table focuses on health risk assessment and does not include information on the variables used to calculate risk, such as exposures and risk values. Table 2-6 is particularly useful when the same populations are exposed to more than one contaminant or multiple concentrations of the same contaminant. The risk results for different contaminants may be entered by listing different chemicals down the left column and their corresponding risks across the same row. Alternatively, risks resulting from different contaminant levels can be entered in the left column when exposures to varied species are occurring with differing concentrations of contaminants.

If an additive effect is suspected, the total carcinogenic or noncarcinogenic risks could then be summed for the population or subgroup. Risk estimates may be modified if either a synergistic or antagonistic effect is expected.

Table 2-7 is a template designed to summarize risks for more than one population using a particular waterbody. This approach allows State agencies to obtain an overall estimate of the risks associated with fishing in a specific waterbody. This type of information may be particularly useful in evaluating the need for an advisory over a large geographic area and for a number of waterbodies.

Geographically based fish advisory efforts may target particular regions or areas based on overall risks for the waterbodies in an area. Waterbody-specific risk data can be used to prioritize efforts and may show concentrations of risk that would not be obvious using small population units as groups for comparison. They may also be used to determine that no action is necessary if the sum of all population risks is negligible. If a geographic approach is used in the development of fish advisories, Section 6, which gives an overview of mapping techniques, should be consulted.

Table 2-7 uses summary information from Tables 2-5 or 2-6 and assumes that State agencies will have focused their attention on a particular aspect of the risk distribution (i.e., central tendency, high-end, or bounding estimates). High-end values are listed in the table because it is recommended that fish advisories be based on highly, but realistically, exposed individuals and risks. State agencies may elect, however, to choose some other portion of the risk distribution.

Table 2-7 also provides data entry areas for three populations surrounding a waterbody (A, B, and C) and for various subgroups within those areas. Data entry areas are provided for cancer, noncancer, and "other" risks. The third variable is provided because some decision-makers may wish to evaluate more than one type of risk in a particular category or use more than one risk value (e.g., liver damage and developmental toxicity). Data entry areas are also provided at the bottom of the table to summarize the risks across populations for the total population and for various subgroups. As with all the tables in this document, State agencies may wish to modify this table to address their specific needs.

State agencies may wish to compare risks at different waterbodies over large geographic areas. Table 2-8 provides a template designed to summarize risk data collected for specific waterbodies and populations. The table may be used to summarize risks to the overall populations or to specific subpopulations using a waterbody. If subpopulation risks are of interest, the format provided in Table 2-8 can be followed with four rows used for each waterbody.

Table 2-8. Risk Summaries for a Geographic Area

Waterbody Location	Risk Estimates Based on High-End Exposures	
	Carcinogenic Effects	**Noncarcinogenic Effects**
Total Risk:		